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ACTA RADIOLOGICA

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EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

CARL KREBS

ANNIVERSARY NUMBER

VOL. 37 MARCH-APRIL 1952 Fasc. 3-4

ACTA RADIOLOGICA

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VOL. 37 MARCH—APRIL 1952 FASC. 3—4

THIS ISSUE IS DEDICATED TO

CARL KREBS

PROFESSOR OF RADIOLOGY AT AARHUS UNIVERSITY ON
THE OCCASION OF HIS SIXTIETH BIRTHDAY, MAY 2ND, 1952,
BY HIS PUPILS AND COLLEAGUES
AS AN EXPRESSION OF THEIR FRIENDSHIP AND
GRATITUDE AND IN ACKNOWLEDGEMENT
OF HIS CONTRIBUTION TO DANISH
RADIOLOGY.

Carl Kruh

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Edited by Jørgen Bichel, Olaf Brøbeck and J. Munck Nordentoft

CARL KREBS

ON HIS SIXTIETH ANNIVERSARY

May 2nd, 1952.

On May, 2, 1952, CARL KREBS' sixtieth birthday, his pupils, past and present, as well as his collaborators feel a natural desire to express to him their reverence and gratitude.

His work and leadership in the Radiological Department of the Aarhus City Hospital and the Radium Centre for Jutland have been of great importance, not only to his own hospital and to radiological science generally, but also to that part of Denmark served by this radiotherapeutic centre.

Over a long period the many contributions from himself and his department have helped to throw light upon the numerous difficult problems relating to experimental cancer research.

After a general medical education, CARL KREBS commenced his radiological career in 1921 as PANNER's assistant in the Radiological Department of the University Hospital in Copenhagen. Almost from the very outset he began to take an interest in experimental cancer research and radiobiology. While working under the stimulating and intuitive leadership of FIBIGER, he seems to have received the impulse to enter upon investigations in this field and he continued his studies of these problems throughout the years. His first paper published in 1925 on »Investigation into the biological effect of filtered and unfiltered X-rays as measured on peas», carried out in collaboration with his good friend LEIF ARNTZEN, was, considering the time of publication, an excellent work bearing witness to fresh initiative and independent thinking.

It was not, however, until 1923, when he was appointed head of the Radiological Department of the Aarhus City Hospital and the Radium Centre for Jutland, that he had occasion to display the exuberant energy which has given rise to the large Institute which he leads to-day.

KREBS' rare gift for persuading institutions, foundations, and municipal authorities to grant funds for scientific research has become almost a legend. His success in these matters is due largely to his joviality, his eloquence, his knowledge of human nature, his ability to substantiate the value of his work and the progress attained; and the money has always carried interest in the form of progress within the field of cancer research.

As his Institute and Laboratory grew, publications by himself or his co-workers saw the light of day. He formed a school of his own and knew how to procure for his pupils working conditions which made their work fruitful. The thesis for his doctorate on »The effect of roentgen irradiation on the interrelation between malignant tumors and their host», published in 1929, formed the starting-point for a large number of subsequent papers by himself and his co-workers within this field of experimental cancer research. Among these later works, it is worth drawing special attention to the studies on leucoses and lympho-sarcomatoses: »The origin of lympho-sarcomatosis and its relation to other form of leucosis in white mice» and »Radiosensibility of the lymphosarcomas» both published in 1930 in collaboration with RASK-NIELSEN and WAGNER, »The radiosensibility of human lymphosarcomas, determined by heterologous transplantation» with F. BUSCH (1931), »Züchtung von Lympho-sarcom in vitro» with B. FABER and »Versuche der Heterotransplantation von Mause-Lymphosarcom» with M. THRANE (1932).

KREBS has also made valuable contributions to other fields of experimental radiobiology. At an early date he began to take an interest in the possible significance of chemical compounds in cancer therapy and their carcinogenic action, no doubt influenced by FIBIGER. Later, he also studied the problem of viruses in cancer research and the question of the building up of immunity: »Experiments with mammalian sarcoma extracts in regard to cell-free transmission on induced tumor immunity» by KREBS, THORDARSON and HARBO, and »Über Röntgenbestrahlung und Adsorption als Methoden der Virusforschung» by KREBS and HARBO.

In addition to his experimental studies KREBS has also published a large number of other papers, of a therapeutic as well as a diagnostic nature, and has, moreover, been a frequent lecturer in connection with the campaigns conducted by the Anti-Cancer League in the propaganda for the early treatment of cancer.

KREBS' extensive work on experimental cancer research and the numerous pupil publications which he has sponsored would not have been possible, if he had not at the same time built up the therapeutic clinic and the laboratory of which he is now the leader.

This has been incident in part, to his activity within the Danish Anti-Cancer-League and the establishment of three radiotherapeutic centres in Denmark and in part, to his activity on the Committee the work of which has resulted in the establishment of the new University in Aarhus. For several years he was a member of the University Board, and as the University gradually expanded, was appointed its first Professor of Radiology.

His social interests have also been fruitful in other directions. He has been chairman of the Aarhus Medical Association and of the Danish

Society of Radiology. He is, moreover, a member of the executive committees of the Northern Association for Medical Radiology and of »Acta Radiologica» and has been and is still a member of the committees of numerous medical and other societies.

CARL KREBS' personality and wide interests have gained him innumerable friends. His sense of humour and ready wit, his learning and eloquence have made him a treasured and popular member of any scientific and social gathering.

On his sixtieth birthday his colleagues want to express their gratitude for his contributions to Danish as well as Scandinavian Radiology; his pupils and collaborators add their thanks for an unfailing interest in their daily work; and they all wish him many years of continued work within that branch of science which has won his heart.

P. Flemming Möller

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FROM THE RADIUM CENTRE FOR JUTLAND, AARHUS, DENMARK
(DIRECTOR: PROFESSOR C. KREBS)

VARIATIONS IN THE GLUCOSE TOLERANCE TEST CURVES IN PATIENTS WITH ENDOMETRIAL CARCINOMA

by

Poul E. Andersen

Although the basic symptomatology and pathology of endometrial carcinoma are well-known, interest is being continually focussed on certain factors. These include hyperplasia of the endometrium, the late menopause, the occurrence of granulosa-cell or theca-cell tumors of the ovary etc., suggesting that the prolonged unopposed action of estrogenic hormones is an important factor in the pathogenesis of endometrial carcinoma.

Diabetes mellitus has been mentioned in the literature as a frequent complication and contraindication to operative treatment. PALMER, REINHARD, SADUGOR & GOLTZ found 16.9 per cent of their patients to be suffering from diabetes mellitus (fasting blood sugars above 120 mg per cent, abnormal glucose tolerance tests, &c., leading to the diagnosis of diabetes). SCHEFFEY & THUDIUM reported 11 per cent diabetics in their series of patients with endometrial carcinoma and comment as follows: »The association between diabetes and carcinoma of the endometrium is not surprising when we consider that the obesity present in so many patients may predispose to or be associated with diabetes.» However, they offer no explanation of the obesity, or of the various other pathologic conditions commonly found in patients with endometrial carcinoma.

In a small and perhaps selected series of patients, Moss found 23 per cent with a manifest, relatively severe diabetes, while 65 per cent had abnormal glucose tolerance test curves (g. t. t. curves); 16 per cent of the patients gave a family history of diabetes.

Submitted for publication Oct. 30, 1951.

In 1949 the author found 5 per cent of his patients to be diabetics receiving insulin treatment and further investigations have revealed many mild cases.

Considering that the incidence of diabetes in the general female population over 35 years of age — according to a survey by SPIEGELMAN & MARKS covering 1.3 million females — is 1.02 per cent, the incidence in patients with endometrial cancer is unduly high even if allowance be made for the factor of obesity.

Only a few authors have investigated the glucose tolerance in patients with endometrial carcinoma and then usually as a diagnostic measure in cases of suspected diabetes mellitus (MOSS; PALMER, REINHARD, SADUGOR & GOLTZ). Curves, both too high and falling too slowly, have been commonly found.

1950 PLATE reported a case of functional uterine hemorrhage in a menopausal woman caused by oestrogenic substances from the adrenal cortex; he found an abnormal g. t. t. curve in a 72-year-old woman suffering from a marked hyperplasia of the endometrium combined with obesity, hypertension and a strikingly youthful general condition, a syndrome commonly encountered in patients with endometrial carcinoma.

These findings suggest a relationship between endometrial carcinoma, mucosal hyperplasias, carbohydrate metabolism and the adrenal cortex and further substantiate the theory of the hormonal cause of endometrial cancer.

Author's Investigations

During the investigation of a large number of patients with endometrial cancer, it was noticed that there seemed to be a difference in the percentage of abnormal g. t. t. curves obtained before and after radium therapy (by the Stockholm method) of corpus cancer (to be published by the author); this caused an investigation into the variations of the g. t. t. curve in these patients. The glucose tolerance test was carried out before treatment was given, shortly after the second application of intracavitary radium and as often as possible 3, 4 or 6 months later (in most cases also 1 to 2 years later). The glucose tolerance test was performed as follows: after 12—14 hours of fasting, 1 g of glucose per kg body weight administered orally in the morning after blood sugar determined; blood sugar determinations every 15 minutes for the first hour and every 30 minutes for the next two hours (method: Hagedorn-Norman Jensen) A rise in the g. t. t. curve above 200 mg per cent was considered abnormal (above 250 mg per cent: markedly abnormal), a rise to a level between 180 and 200 mg percent as questionable abnormal, especially if the fall was slow and protracted, while curves not exceeding 180 mg percent were considered normal.

The Material

35 patients were submitted to a series of glucose tolerance tests. 22 had no signs of active tumor growth, while the remaining 13 patients either had, or later revealed, distant metastases, local recurrences or invasion of the parametria. The variations in the g. t. t. curves are shown in table 1. 10 patients with markedly abnormal (A) curves before treatment showed normal (n) curves on one or more occasions after treatment (A to n). 7 patients with abnormal (a) curves also showed normal curves (a to n). In 2 patients the curve changed from markedly abnormal to questionably abnormal (A to q) and in 3 patients from markedly abnormal to less abnormal (A to a). We have not been able to demonstrate active tumor growth in any of these patients, but we admit that the patients have only been followed-up for about $1^1/_2$—2 years. However, judging from our experiences and laboratory findings we have some reason to believe these patients to be cured. The group of patients with active tumor tissue showed the following variations (using the above abbreviations): 7 patients a—A, 2 A—A, 2 a—n—a, 1 q—A and 1 q—q; all these patients have been re-admitted either with local recurrence, vaginal metastases or progression in the parametria.

Table 1

Change of the Glucose Tolerance Test Curve Following Radium Treatment

(A: markedly abnormal; a: abnormal; q: questionably abnormal; n: normal.)

Patients *without* demonstrable tumor		Patients *with* demonstrable tumor	
A to a	3	A to A	2
A to q	2	a to A	7
A to n	10	a to n to a	2
a to n	7	q to A	1
		q to q	1

Thus a considerable difference in relationship to radium treatment exists between patients with recurrences and other forms of progression and patients without demonstrable active tumor growth.

The variations have been observed as often in obese as in normal or thin patients and in preclimacteric as in postclimacteric women. Similar changes of the g. t. t. curve may be seen when weight is being lost, but the weight of these subjects has in every case been fairly constant, the

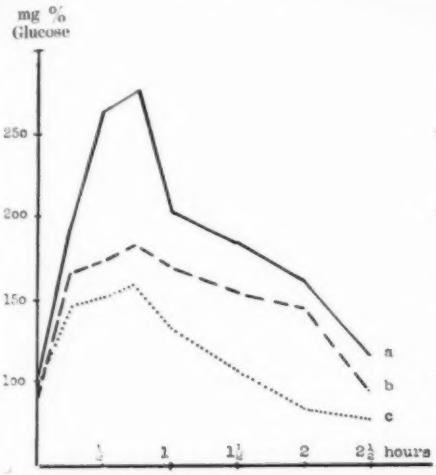

Figure 1. Case 1. Curve a: before treatment; b: after treatment; c: 11 months later.

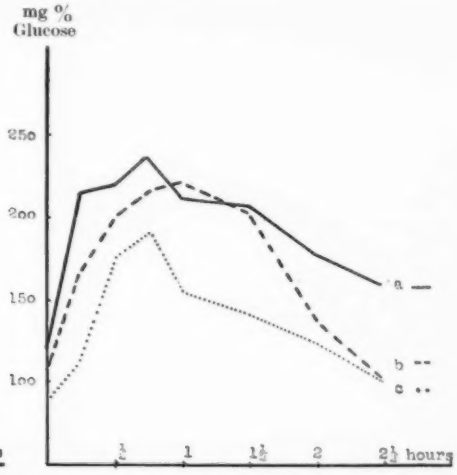

Figure 2. Case 2. Curve a: before treatment; b: after treatment; c: 2 months later.

variation seldom amounting to more than 1—2 per cent during the period of investigation.

For comparison a number of patients suffering from cancer of the cervix uteri have been submitted to glucose tolerance tests, before radium treatment, after radium treatment and after completion of the whole course of radium and roentgen treatment. In 9 out of 14 patients the course of the g. t. t. curve, which was normal, remained unchanged, while slightly abnormal curves in 3 patients also remained unchanged at the following tests. One patient showed a questionable difference in the course of the g. t. t. curve while another had not been fasting at the first test.

While no definite change in the g. t. t. curve can be demonstrated in patients suffering from cervical cancer, the variation of the curve in cancer of the body of the uterus seems to be a well-established fact.

Case 1: A woman, aged 59, was admitted in Nov. 1950 with a typical adenocarcinoma of the corpus uteri. Not obese (weight 57.5 kg, height 165 cm); the clinical examination revealed no pathologic conditions except the corpus cancer and a mild hypertension. The sedimentation rate was 8 mm/1 hour, her blood counts, hemoglobin and other analyses also normal. The patient had typical radium treatment (Stockholm method) and the g. t. t. curve was determined before, after, 4 months and 11 months after the treatment. Figure 1 shows the variation of the curve. (The curve 4 months after treatment has been omitted; it was between b and c.) At the last follow-up examination the patient was quite well and no tumor could be found. She had gained a little weight.

Case 2: A woman aged 64, with a typical case of adenocarcinoma of the corpus uteri. Obese (weight 80 kg, height 164 cm); no further abnormalities except cholelithiasis, slight hypertension and a questionable infiltration of the right parametrium for which a supplementary course of roentgen treatment following radium therapy, was given. The g. t. t. curve was determined as usual and figure 2 shows its variation.

The explanation of the variation in the glucose tolerance test curve is at present difficult and no safe conclusion can be drawn from this relatively small material. The following two theories seem to be the more probable possibilities: 1) the tumor produces a hormone with an inhibitory action on insulin; the inhibitory effect is abolished with the destruction of the tumor, but is increased by its growth. 2) some other hormonal unbalance exists and is influenced by the treatment given. It may be of interest to recall in this connection that MEISSNER & SOMMERS produced an abundant endometrial hyperplasia resembling a precancerous condition by treating post partum diabetics with stilbestrol and progesterone. But whatever the etiology of this variation of the glucose tolerance test curve we hope that it will enable us to detect recurrences at an early stage. This should be of great value in these usually obese patients in whom bimanual examination is often very difficult.

SUMMARY

The author reports the variations in the glucose tolerance test curves in patients with endometrial carcinoma.

ZUSAMMENFASSUNG

Der Verfasser berichtet über die Variationen der Glukosebelastungskurven bei Patienten mit Endometriekarzinom.

RÉSUMÉ

L'auteur rend compte des modifications de la courbe d'hyperglycémie provoquée chez des femmes atteintes de cancer de l'endomètre.

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FROM THE ROENTGEN CLINIC (DIRECTOR: AAGE WAGNER), AARHUS COUNTY HOSPITAL, DENMARK

SUPERNUMERARY URETER WITH ECTOPIC ORIFICE

Report of Two Cases

by

Ulla Arlien-Soborg

Congenital anomalies of the kidneys and ureters are not uncommon and occur almost as frequently in males as in females.

Such anomalies should obviously always be borne in mind during diagnostic considerations, and this is surely also done when they can be demonstrated in ordinary pyelograms and urograms; but it should also be realized that certain anomalies, which may escape recognition in ordinary roentgenograms, may be visualized by special roentgenographic methods.

Here I think, in particular, of the abnormal ureteral orifices, which are well-known phenomena to the surgeon but perhaps not to the radiologist.

However, these anomalies are not at all rare. In 1928 THOM collected 128 cases, of which the majority were found in females. There may be one, two, three or even — as in two of THOM's cases — four ureters with extravesical orifices in the same patient. In the male, these ureters open into the prostatic urethra, a Cowper's gland, seminal vesicle, ejaculatory duct, or vas deferens. In the female, the opening is into the urethra, vestibule of the vagina, tube, or uterus. — All these organs lie in close relation to or are developed from the Wolffian and Gartner's[1]

[1] The Danish anatomist, HERMAN TRESCHOW GARTNER (1785—1827), discovered ductus epoophorus longitudinalis and described it for the first time in 1822. A subsequent description appeared in the Publications of the Royal Danish Academy of Sciences. He was awarded the Silver medal of the Academy for his discovery (personal communication from Prof. EDV. GOTFREDSEN).

Submitted for publication, Oct. 30, 1951.

ducts. In either sex, the ureter may also terminate in the rectum or in some part (other than the normal) of the bladder.

Embryologically, it is not difficult to imagine how most of these abnormal orifices may arise; but in the cases of several the origin is still unclear.

Proximally, ectopic ureters may end in a kidney — possibly in a supernumerary kidney — or they may end blindly.

They are not rarely malformed. Angulations and spiral twists may be present, or there may be dilatations and/or stenoses, which may in turn cause stasis with calculus formation and infection.

These conditions may give rise to clinical pictures which are very difficult of interpretation if the described anomalies are not borne in mind, especially if at the same time completely normal kidneys and ureters are present, which is not infrequently the case.

A symptom which should always be suggestive of the presence of a ureter with an ectopic opening is urinary incontinence. In females, this anomaly will often result in incontinence, whereas it is rare in males because the abnormal ureters always open proximally to the triangular ligament of the urethra where Gartner's ducts end. On the other hand, the presence of an abnormal ureter is much more difficult to diagnose in males than in females.

At the County Hospitals at Aarhus and Odder we have recently seen two cases of incontinence due to ectopic ureteral openings. In one of the patients the condition was easily recognized (fig. 1), whereas the diagnosis caused difficulties in the case of the other patient, inter alia, because she also had pyonephrosis of the kidney of the same side (which had a normal ureter), a perinephritic abscess, and — as appeared later — an empyema of the supernumerary and blindly-ending ureter.

Case I. A girl, aged 9 years, had been hospitalized at the age of 3 months for »vaginal discharge». The catheterized urine was clear, but pus could be expressed from the urethra alongside the catheter. Infection of a paraurethral gland was suggested. The symptoms subsided in the course of a fortnight and the patient remained symptom-free for 12 months. She then began to suffer from constant »vaginal discharge» and occasional incontinence. Two months prior to the last admission she developed attacks of fever and pain in the lower part of the abdomen, accompanied by increased discharge. On admission, an elongated mass could be palpated in the vaginal wall; on pressure, this mass discharged pus through a small orifice in the distal part of the urethra. Through this orifice a catheter was inserted; it could be passed up for 25 cm. Direct pyelography revealed a normal pelvis and a normal ureter, around which the catheter, inserted through the opening of the fistula, apparently twisted (fig. 1). There was no renal pelvis at the upper end of the catheter. — The catheter was left in place for some days. The fever subsided, but so much fluid flowed from the catheter that a bottle was necessary for its collection.

After the subsidence of the fever the supernumerary ureter was removed. At the upper end it ended blindly without any connection with the renal pelvis. It twisted

Fig. 1. Case 1. A thick catheter is inserted through the orifice in the distal part of the urethra. The renal pelvis is filled with contrast through a narrow catheter in the normal ureter.

spirally around the normal ureter. It is a peculiar but unexplained fact that spirality is a marked characteristic of anomalies arising from the Wolffian ducts. The pyelogram gave rise to a suspicion of a spiral course of the ureter, and this suspicion was confirmed at operation. The postoperative course was uneventful. A microscopic examination showed a tubular cord, made up as a ureter and without any renal tissue at the upper pole. The wall was inflamed.

Case 2. A married woman, aged 41 years, had always suffered from a distressing urinary incontinence. — She had previously undergone Shauta-Wertheim's operation and strumectomy for exophthalmic goiter.

Fig. 2. Case 2. Urography. Slightly dilated pelvis and ureter. The kidney is displaced laterally.

Fig. 3. Case 2. Contrast-filled supernumerary ureter ending distally in the urethra.

The patient was admitted with high-grade fever and pain in the left lumbar region. Urography showed lateral displacement of the left kidney, effacement of the psoas shadow, possibly a slightly dilated renal pelvis, and some indication of ureteral stasis (fig. 2). The roentgen diagnosis was perirenal abscess (? pyonephrosis). Operation revealed

a perirenal abscess and also an orange-sized pyonephrosis in the upper renal pole and a small pyonephrosis in the lower pole, but only one ureter.

After operation, fluid injected into a drain inserted into the operative wound reappeared through the urethra, for which reason it was supposed that the perirenal abscess had perforated the urethral wall.

Some time after the operation fever and pain in the left side recurred, accompanied by »urinary incontinence». It appeared that the catheterized urine was normal but that the voided urine often contained pus. A gynecological examination revealed a small orifice, through which fluid could be expressed, situated distally in the urethral wall, and a catheter inserted into the opening could be passed up for about 15 cm. A contrast medium was injected and a cul-de-sac, the thickness of a thumb and 15 cm long, was disclosed; it extended through the lumbar region to the level of the fourth lumbar vertebra. The pouch was extirpated and since then the patient has not had incontinence. Microscopic examination in this case also revealed a cord, made up as a ureter and with inflammation of the wall.

Both patients had a supernumerary ureter with an ectopic opening. In the first patient it ended blindly at the upper end and the fluid, which escaped from it and had been described as a discharge or as urine, must have been an inflammatory product.

The second patient had probably a double pelvis and the abnormal ureter must have been connected with the upper one, but this had not been noticed at operation. That the orange-sized pyonephrosis had escaped recognition in the urogram must have been due to the fact that the renal tissue was destroyed to such an extent that no excretion of the contrast medium could take place. The abnormal ureter had passed unnoticed at the operation and had been cut; it was through this ureter that the fluid which was injected into the drain gained its way to the urethra, and not through a perforation caused by the perirenal abscess. The incontinence, which had persisted for many years, is also in favour of the assumption of such a connection, as the ureteral epithelium is non-secreting, and only in the presence of an inflammatory process in the wall can a blindly ending ureter »secrete» fluid, as was seen in case 1.

In case 2, the ureter with the ectopic orifice was the cause, not only of the incontinence, but also of the alarming clinical picture. The considerable dilatation both of the ureter and the upper renal pelvis is in favour of the assumption of a stenosis in the lower portion of the ureter. Stasis and an ascending infection had developed, the latter spreading to the lower pelvis and the perirenal tissue.

It may be exceedingly difficult to find an ectopic ureteral orifice in the urethra. It may be hidden among the folds of the mucosa. If such an anomaly is suspected, which, as previously pointed out, should always be the case in the presence of incontinence in females, the injection of a dye, followed by probing and the injection of contrast medium, is indicated.

Peri-urethral inflammatory processes in females may also have their origin in urethroceles and diverticula arising from the urethra, in small glands in the urethral wall, in Skene's ducts (which may terminate either intra- or extraurethrally), and in persisting Wolffian ducts (Gartner's ducts). These conditions may usually be distinguished roentgenographically.

SUMMARY

A supernumerary ureter ending extravesically was present in two patients. In both cases the condition gave rise to fever and, in one of the patients, to »vaginal discharge» and, in the other, to urinary incontinence.

The methods of diagnosis and treatment are discussed.

ZUSAMMENFASSUNG

Bei 2 Patienten wurde ein überzähliger Ureter mit extravesikalem Ende gefunden. In beiden Fällen entstand durch diesen Harnleiter Fieber sowie bei dem einen Patienten vaginaler Fluor, und bei dem anderen Urininkontinenz.

Diagnostische und therapeutische Methoden werden diskutiert.

RÉSUMÉ

Deux malades ont présenté un urétère surnuméraire à écoulement extravésical. Dans les deux cas cette anomalie provoquait de la fièvre. Chez l'une des malades il y avait »perte vaginale» et chez l'autre incontinence d'urine.

Les méthodes visant le diagnostic et le traitement sont discutées.

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MYELOSCLEROTIC ANEMIA

Report of a case

by

Poul Bastrup-Madsen

The purpose of this paper is to review in detail the clinical picture of a case of myelosclerotic anemia with marked roentgenographic changes.

In myelosclerosis the normal blood-forming elements of the bone marrow are replaced by fibrous or bony tissue. As a result, compensatory foci of hemopoiesis develop in other organs of the reticulo-endothelial system. Splenomegaly is a prominent feature, and the disease may consequently be difficult to differentiate from other disorders with splenomegaly. Even though a rather comprehensive casuistic literature on myelosclerosis has gradually become available, one still feels justified in calling attention to this rare condition, because the methods of treatment (roentgen irradiation, splenectomy) which have proved successful in many other forms of splenomegaly can be dangerous in cases of myelosclerotic anemia.

The disease was first described by HEUCK in 1879, since when cases have been reported under a great variety of names; the most common of these are »leuco-erythroblastic anemia», »chronic non-leukemic myelosis», and »myelofibrosis associated with a leukemoid blood picture». Extensive surveys of the literature have been published by ERF & HERBUT and CRAIL, et al., and the Scandinavian literature on the subject has recently been reviewed by PINHOLT ANDREASEN, and JOHANNESSEN.

Previously, the diagnosis could not be definitely established excepting at autopsy. Experience gained during the last 10—15 years in intravital examinations of hemopoietic organs, however, has made it possible to make the diagnosis during life.

Myelosclerosis may be symptomatic or idiopathic. Metastatic carcinoma in the bone marrow is, perhaps, the most common cause. Furthermore, benzene, fluorine, lead, arsenic and phosphorus poisining, as well as irradiation and radioactive substances, are believed to be definite

Submitted for publication, Oct. 30, 1951.

causal agents. Myelosclerosis has also been described in cases of chronic miliary tuberculosis and of syphilis. In addition, there is the idiopathic form of myelosclerosis or osteopathia condensans disseminata, which will be mentioned here.

Signs and symptoms: Clinically, the disease is characterized by anemia and discomfort caused by the enlargement of the liver and spleen. There may be pain in the bones. However, there are often no osseous symptoms, even in the presence of extensive bone changes; a tendency to spontaneous fractures has never been observed.

The anemia, which is frequently normocytic and normochromic, is variable in degree. In some cases even moderate polycythemia has been found in the early stages. There are no signs of iron deficiency or lack of the antipernicious anemia principle. The leukocyte count is normal or may in rare cases be reduced or increased. A very characteristic feature of the disease is the occurrence of immature cell forms, both nucleated red cells, myelocytes, and sometimes also megakaryocytes in the peripheral blood. For this reason the disease may easily be mistaken for chronic myeloid leukemia.

The examination of the *bone marrow* is of great importance for the exclusion of leukemia. Frequently, great difficulty is experienced in obtaining a sample by bone marrow biopsy, since aspiration will often yield only pure blood. Sometimes the bone may be very hard and difficult to penetrate. However, it is important to obtain a sample consisting of bone marrow elements in order to exclude leukemia. Puncture of various bony parts (the iliac crest, sternum, spinous process of one of the vertebrae) should therefore be attempted until a satisfactory sample is obtained. The difficulty in securing a sample is, in itself, a very suggestive diagnostic hint. The smears reveal a hypocellular bone marrow containing all the normal precursors of the various blood cells, with no abnormal cell forms present. A confident opinion may be expressed after demonstrating the fibrous nature of the marrow in a histological section. Material for such an examination may be obtained by bone marrow biopsy, but a sample of marrow obtained by trephine (for example, from the iliac crest) must often be cut and examined as a section.

The demonstration of *extramedullary hemopoietic foci* lends further support to the diagnosis. The greater proportion of the hemopoiesis occurs in extramedullary sites, especially in the enlarged spleen and liver. Needle biopsy of these organs therefore constitute an important part of the examination.

The changes observed in the *roentgenograms of the bones* are variable. The distribution of the pathological processes is irregular. The compact substance of the bones may be thickened. The roentgenographic appearance of the spongiosa depends on the predominance of either sclerotic

or fibrous processes; the latter cannot, actually be seen in the roentgenograms. Sclerotic processes resembling cancer metastases are often scattered over many parts of the skeleton.

Course: The anemia is progressive but the course is slow. After a protracted period with slight anemia a time comes when blood transfusions must be given. Usually, the disease terminates with a picture of a pancytopenia.

Report of Case

A 67-year-old man had, since the age of 17 years, had a tendency to eczema, most frequently localized to the backs of the hands; occasionally there had been a generalized eruption. He had otherwise been in good health until at the age of 62 years (1946) he was admitted to hospital with fever of unknown origin and slight edema of the legs. The temperature returned to normal in the course of 5 days. After this, his principal complaint was of epigastric oppression and slight dyspnea.

Physical examination: Slight cyanosis, slight dyspnea and some edema of the legs were observed. A systolic murmur was heard over the heart. The liver extended 4 cm, and the spleen 10 cm, below the costal margin.

Laboratory examination: Blood: Hemoglobin 64 %, erythrocytes 2,600,000, color index 1.23, leukocytes 4,400; smear: neutrophilic polymorphonuclear cells 82 %, lymphocytes 16 %, monocytes 2 %; a few normoblasts were present; the red blood cells showed anisocytosis, poikilocytosis, and polychromasia. There were 12 ‰ reticulocytes. The fragility of the red cells was normal. The serum protein values were normal: 5.8 gm per 100 ml (albumin 3.81 gm, globulin 1.99 gm). The Takata-Ara test was normal; the serum citric acid values were also normal. Bone marrow: Sternal puncture was attempted three times. The bone was very massive; twice the aspiration yielded only pure blood, but the third time the sparse sample obtained, contained some normal marrow elements (P. Kirketerp). Splenic puncture: In addition to normal types of splenic cells, promyelocytes, neutrophilic myelocytes, metamyelocytes, nucleated red cells in various stages of development, and a few megakaryocytes were found (J. Bichel). The roentgenogram of the lumbar spine showed normal conditions. The electrocardiogram was normal.

Treatment with a concentrated liver preparation (Hepsol fortior) did not produce any beneficial effect on the hemoglobin level.

During the next few years he complained of progressive fatigue, dyspnea, cough, and a tendency to eczema of the legs. Five years later (1951) he was readmitted, this time for congestive heart failure.

Physical examination revealed some dyspnea and cyanosis. There was evidence of cardiac enlargement. Marked edema of the lower extremities was present. The liver extended 8 cm, and the spleen 12 cm, below the costal margin. The thyroid gland was normal.

Laboratory examination: Chest roentgenograms showed cardiac enlargement and pulmonary congestion, and electrocardiography a 3 : 1 auricular flutter. The urine was repeatedly negative.

Blood: Hemoglobin 72 %, erythrocytes 3,550,000, color index 1.04, leukocytes 6,600; smear: myelocytes 3 %, stab cells 20 %, neutrophilic polymorphonuclear cells 60 %, lymphocytes 17 %; some nucleated red cells were observed. There were 6 ‰ reticulocytes; thrombocytes 221,000. Serum iron 0.125 mg per 100 ml; serum protein 5.98 gm per 100 ml (albumin 3.71 gm, globulin 2.27 gm). The Takata-Ara test, thymol turbidity, and serum citric acid showed normal values. Plasma color index 8

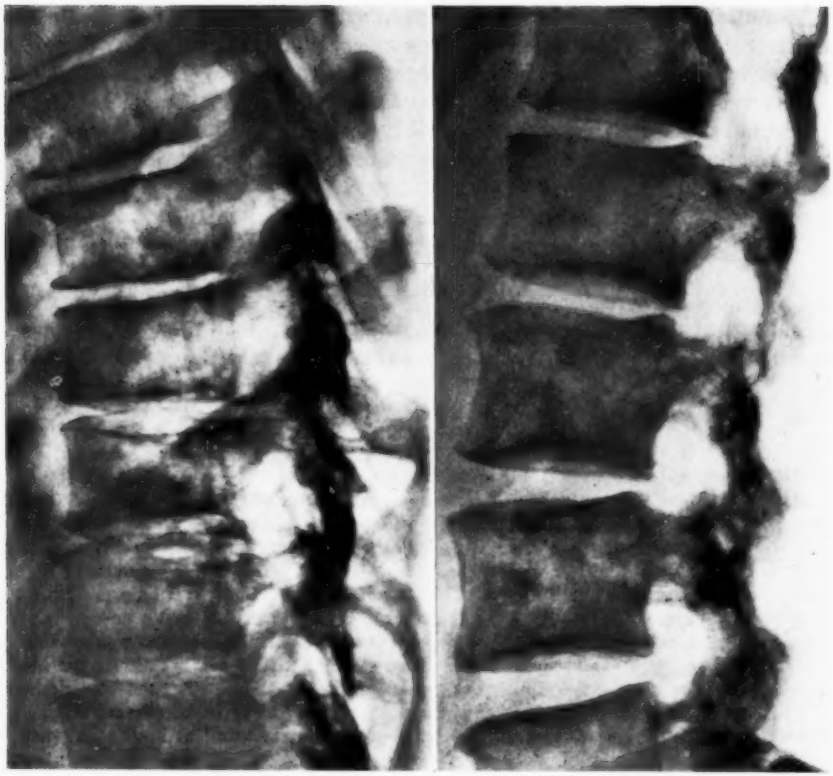

Fig. 1. Fig. 2.

Figs. 1 and 2. Extensive, spotted, confluent densities in the thoracic and lumbar spine.

(normal). Sedimentation rate 22 mm/1 hour. Serum calcium 10.3 mg per 100 ml; serum phosphorus 6.2 mg per 100 ml. Alkaline phosphatases in the serum 9.5 Buch units (normal), acid phosphatases 1.8 Gutman units (normal). Bone marrow: From the sternum, blood only could be aspirated. From the spinous process of the fourth lumbar vertebra a sparse amount of marrow was obtained; it was hypocellular but otherwise normal.

Roentgen examination: In the thoracic and lumbar regions of the spine (figs. 1 and 2) extensive, fairly marked, spotted, confluent densities were found. A roentgenogram of the pelvis showed a pronounced sclerosis in the body of the ilium on both sides as well as medially in the ala of the ilium, and in the upper portion of the sacrum. There was sclerosis of a spotted character in the pubic bone and confluent sclerotic areas in the ischium. Diffuse and spotted osteosclerosis was observed in the upper portion of both femora. The femora and the bones of the leg had a thick cortex. In the heads of the humeri some small sclerotic spots were present, and in the distal end of the right radius there was an almond-sized sclerotic density.

Clinical course: During treatment with a salt-free diet and rest in bed, the edema subsided and the general condition improved considerably. Administration of iron did not produce any favourable effect on the anemia.

Discussion

A man, 67 years of age with congestive heart failure had for 5 years suffered from moderate anemia with splenohepatomegaly. A diagnosis of myelosclerotic anemia was made during life by reason of the following signs: (1) normochromic, normocytic anemia, (2) occurrence of normoblasts and immature leukocytes in the blood, (3) hypocellular bone marrow without abnormal cell forms, (4) extramedullary hemopoiesis in the enlarged spleen, and (5) sclerotic changes in the roentgenograms of the bones.

The bones of the lower extremities had a very thick cortex. However, it cannot be stated definitely if this was a pathological feature, as fairly wide individual variations exist as regards the thickness of the cortex.

The course of the disease was slow. The myelosclerotic anemia had been diagnosed 5 years previously. At that time the liver and spleen were considerably enlarged, which indicates that the disease must have started at least a couple of years before that time. At the last examination the anemia was still moderate. Nothing can be said about the development of the pathological processes in the bones during the 5 years which had elapsed since the diagnosis was made since, at the first examination, roentgenograms were taken only of the lumbar spine. In these roentgenograms no abnormalities were visible. Five years later there were extensive osteosclerotic processes in this region. Thus, some progression must have occurred during this period.

Other possible diagnoses will be enumerated. Owing to the occurrence of the immature cells in the blood, a diagnosis of chronic myeloid leukemia must be considered. However, the hypocellular bone marrow is against leukemia. It is of paramount importance not to mistake myelosclerosis for leukemia as roentgen irradiation of the spleen may result in an aggravation of the anemia.

The hepatic and splenic enlargement might be suggestive of Banti's syndrome. The facts that the tests of hepatic function were normal, and that there were no signs of hypersplenism is against this diagnosis. Furthermore, there is no reason to expect immature cell forms in the blood, extramedullary hemopoiesis, or still less, osteosclerotic changes in Banti's syndrome.

Congenital hemolytic jaundice can be excluded owing to the normal fragility of the red blood cells.

The patient had heart disease, and the enlargement of the liver and spleen might therefore be due to congestive heart failure. However, the

cytological changes in the blood, bone marrow, and spleen cannot be explained thus. There might, perhaps, in this case be some connection between the myelosclerotic anemia and the cardiac disease, but only in such a way that the former would have aggravated the latter. The chronic anemia might have promoted the myocardial degeneration. The enlarged liver and spleen, due to the myelosclerosis, might have exerted a pressure on the veins and thus, together with the cardiac insufficiency, been a contributory factor in the tendency to edema of the legs.

The marble-bone disease of Albers-Schönberg can be excluded on account of the age of the patient. This condition is almost invariably recognized before puberty, while myelosclerosis occurs in middle and late life.

The extensive sclerotic changes in the bones are highly suggestive of bone metastases, which may be seen in carcinoma of the thyroid gland, hypernephroma, and carcinoma of the prostate. The fact that the values of the acid phosphatases in the serum were normal weighs against carcinoma of the prostate. In addition, such extensive metastases will usually cause considerable pain. As the osteosclerosis was the primary lesion as compared with the anemia and the extramedullary hemopoiesis, the osteosclerosis must have been present for at least 6—7 years. This duration of the disease is against a diagnosis of osteosclerotic bone metastases.

Nothing can be said about the etiology of this case. There was no past history of poisoning by substances which might have given rise to myelosclerosis. The patient had always had a tendency to eczema, but it is impossible to say if any connection exists between his allergic state and the myelosclerosis.

Treatment and Prognosis

In the treatment of myelosclerotic anemia the only valuable therapeutic measure is blood tranfusions. Administration of iron and liver is ineffective. Splenectomy is valueless and usually fatal as the spleen is generally an important site of hemopoiesis. It has occasionally been stated that splenectomy may be indicated when signs of hypersplenism (anemia, leukopenia, and thrombopenia) are present. Even though splenectomy may give temporary relief in such cases, I believe that this operation is always contra-indicated in myelosclerosis, and that it will inevitably hasten death. All the time it should be borne in mind that in myelosclerotic anemia the spleen is a very important hemopoietic organ, and that the sclerosis of the bone marrow is a progressive process.

The disease will inevitably lead to death but the course may be very slow. Some patients have survived for a number of years. The prognosis depends on the effectiveness of extramedullary compensation for the

hypofunctioning bone marrow. For the outlook it is of great importance that therapeutic measures (such as roentgen treatment and splenectomy) which may interfere with the extramedullary hemopoiesis are avoided, and this in turn demands that the proper diagnosis be made at an early stage of the disease.

SUMMARY

A case of myelosclerotic anemia diagnosed during life in a 67-year-old man is reported. Normocytic, normochromic anemia with nucleated red cells and myelocytes in the blood was present. The liver and spleen were markedly enlarged. In a sample obtained by splenic puncture, signs of extramedullary hemopoiesis were observed. Roentgen examination revealed a diffuse sclerosis of certain bones. It is emphasized that it is important to avoid therapeutic measures which may interfere with the compensatory extramedullary hemopoiesis.

ZUSAMMENFASSUNG

Ein Fall von myelosklerotischer Anämie wird berichtet; er wurde bei einem 67jährigen Mann während dessen Lebenszeit diagnostiziert. Man fand eine normozytische, normochromische Anämie mit kernhaltigen roten Blutkörperchen und Myelozyten. Leber und Milz waren bedeutend vergrössert. In einer durch Milzpunktion erhaltenen Gewebeprobe wurden Anzeichen von extramedullärer Hämatopoese beobachtet. Röntgenuntersuchungen ergaben diffuse Sklerose gewisser Knochen. Es wird hervorgehoben, dass es notwendig ist, alle therapeutischen Massnahmen zu vermeiden, die auf die kompensatorische extramedulläre Hämatopoese störend einwirken könnten.

RÉSUMÉ

Présentation d'un cas d'anémie myélosclérotique chez un homme de 67 ans, diagnostiquée de son vivant. Il s'agit d'une anémie normocytaire et normochrome avec des hématies nucléées et des myélocytes dans le sang. Le foie et la rate étaient considérablement augmentés de volume. Dans un prélèvement par ponction splénique on retrouve les signes d'une hémopoièse extramédullaire. La radiographie révèle une sclérose diffuse de certains os. Il est important, souligne l'auteur, d'éviter des mesures thérapeutiques susceptibles de nuire à l'hémopoièse compensatrice extramédullaire.

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LEUKEMIC MYELOMATOSIS (PLASMA CELL LEUKEMIA)

A Review with Report of Four Cases

by

Jörgen Bichel, Poul Effersøe, Harald Gormsen, and *Niels Harboe*

The plasma cell neoplasias in human pathology are: (1) Myelomatosis (multiple myeloma), (2) solitary osseous myeloma, and (3) extramedullary plasmocytoma. All these neoplasias are fairly rare, myelomatosis being the most common and solitary osseous myeloma the most uncommon. Cases of myelomatosis may be aleukemic, subleukemic, or — in extremely rare cases — leukemic, and there are gradual transitions between these conditions. Leukemic myelomatosis is called plasma cell leukemia by many authors.

As leukemic myelomatosis is seldom encountered, reports are submitted of four cases, and on the basis of these and a review of similar cases previously reported the characteristics of the condition are discussed.

Case 1. No. 3607/50 a woman, aged 62, was admitted to the Radium Centre, Aarhus, on October 17, 1950; previously in good health; during the fortnight before admission had suffered from increasingly severe nausea, dizziness, fatigue, dyspnea, and epigastric pain. On admission she was in a toxic condition, delirious at intervals, slightly cyanotic, and dyspneic; the mucous membranes were dry and the temperature high.

Physical examination revealed enlarged cervical, axillary, and inguinal lymph nodes, ranging in size from a hazelnut to a walnut; no enlargement of the liver or spleen;

Aided by grants from the Anders Hasselbalch Anti-Leukemia Foundation, the Lady Tata Memorial Trust, C. P. Schepler and Wife's Bequest (the Irma Foundation), the Ella Sachs Plotz Foundation, and the Tuborg Foundation.

Submitted for publication, Oct. 30, 1951.

no angina or gingivitis and no signs of hemorrhagic diathesis; no protein in the urine. Blood urea: 84 mg%; blood bicarbonate: 30 mEq. The sedimentation rate was 22 mm/hour; Hb. 76 %, RBC 3,370,000; WBC 78,000; thrombocytes 134,000.

During the next four days the leukocyte counts increased steadily to 175,000. The blood picture was quite unusual, 99 per cent of all the leukocytes being large (from 10 to over 30 μ), rounded or slightly oval cells, with large round eccentric nuclei of a moderately fine chromatin structure; no cartwheel structure; indistinct nucleoli. The cytoplasm was deep blue, often with a clear zone opposite the eccentrically placed nucleus and non-granular, but occasionally contained vacuoles (fig. 1).

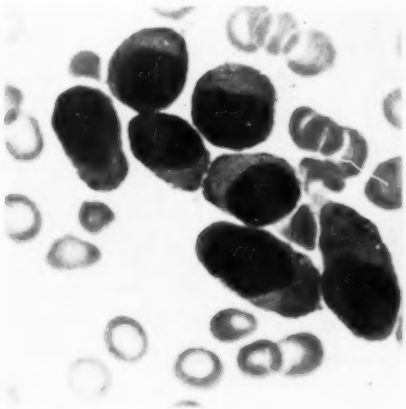


Fig. 1. Plasma cells from the peripheral blood.

A specimen from a cervical lymph node, obtained by needle biopsy, contained numerous cells of the same type as those seen in the blood. Bone marrow smears, obtained by sternal aspiration, also revealed a large number of cells of this type, some being transitional forms to more typical bone marrow plasma cells.

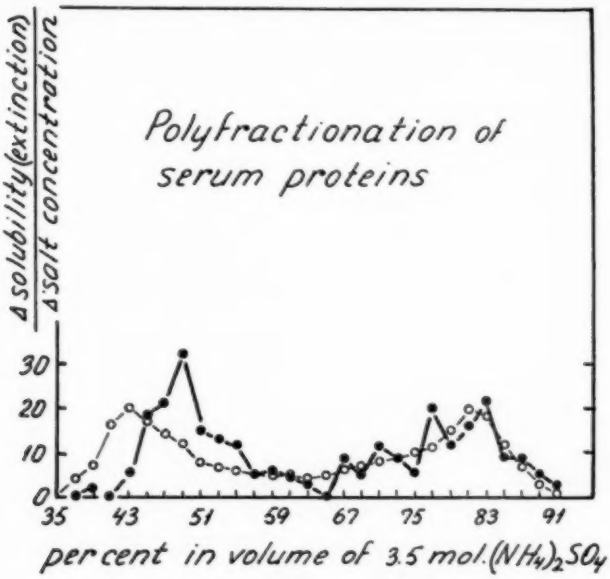
The patient was given a blood transfusion, penicillin and glucose saline but deteriorated rapidly, became comatose, and died in a state of hyperpyrexia four days after admission. Unfortunately, owing to her condition, roentgenograms of the bones could not be taken.

Autopsy revealed, inter alia, enlarged grayish-red, hazelnut-sized lymph nodes, particularly in the mesentery. The spleen was also moderately enlarged (310 g). No circumscribed areas of destruction were found in the bones examined (the skull, femora, sternum, thoracic and lumbar vertebrae and several ribs). The bone marrow showed generalized hyperplasia. The histological examination revealed massive infiltrations of plasma cells and transitional forms between plasma cells and large atypical cells in the organs, especially in the lymph glands, spleen, liver, and kidneys. The infiltrating cells were of the same type as those observed in the blood and bone marrow in vivo.

Analysis of the serum proteins: A determination of the serum proteins by fractionation (method of Henriques and Clausen) was carried out. The results were as follows: Total proteins 6.4 per cent, albumin 4.7, and globulin 1.7. A second determination two days later showed total proteins 6.2 per cent, albumin 5.1, and globulin 1.1.

The serum proteins were also analyzed by a salting-out method, the so-called polyfractionation (EFFERSOE). By it the serum proteins were salted out by ammonium sulfate solutions of varying strength. After sedimentation (centrifugation) of the precipitated protein, the absorption of ultraviolet light in the supernatant fluid, which contained the proteins soluble in the various salt concentrations, was determinated spectrophotometrically (see diagram).

Examined in this way, the patient's serum revealed the presence of both normal total protein, normal total albumin, and normal total globulin; within the range of the globulins there was almost no precipitation corresponding to the first part of the curve, whereas there was a definite pathologic increase within the 49—53 interval, with a maxi-



○ = normal cases. ● = pathologic cases.

Diagram. — Abscissa: Ammonium sulfate concentration. Ordinate: The amount of precipitated protein in each salt concentration interval, determined as the difference between the extinction values of two successive precipitations. The thin line indicates the average curve for 20 normal men and women. The thick line is the patient's curve.

mum precipitation at 49. — This picture is definitely abnormal and in accordance with the diagnosis of myelomatosis or plasma cell leukemia.

Before the electrophoretic analysis, the serum samples were dialyzed at 5° C. against a buffer solution (pH 7.7) consisting of sodium phosphate, ionic strength 0.1, and sodium fluoride, ionic strength 0.1.

The electrophoresis was carried out for 6 hours in a Tiselius apparatus at 0.5° C. The potential gradient was 5.01 volts/cm. The difference between the refractive indices of the solution examined and the buffer was = 0.00264.

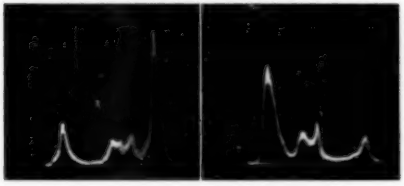


Fig. 2. Electrophoretic patterns. a_1 and particularly a_2 were somewhat increased. The γ component contained almost no gamma of normal type, but was made up of a homogeneous component of a type often found in myelomatosis.

Relative Protein Concentration (%)

Albumin	49.5	normal	56
α_1	8	—	4
α_2	13	—	6
β	15.5	—	16.5
γ[1]	14	—	17.5

Case 2. 2209/44 a woman, aged 66, was admitted to the Radium Centre, Aarhus, from August 23 to October 7, 1944 and from December 12, 1944, to February 6, 1945. Death ensued on February 15, 1945.

During the year prior to the first admission she had had progressive fatigue, and during the previous few months frequent attacks of epistaxis, but no pain. The liver and spleen extended a hand's breadth below the costal margin. No lymph node enlargement.

Bone roentgenograms: No destruction.

Urine: Absence of proteinuria, notably no Bence-Jones proteinuria.

Blood examination (on first admission): Blood urea 38 mg%; W. R. negative; S. R. 165 mm/hour, Hb. 48 %, RBC 1,840,000, WBC 8,400; differential count: pol. neutro. 12 %, band forms 5 %, metamyelocytes 4 %, neutrophilic myelocytes 2 %, eosinophils 2 %, lymphocytes 22 %, monocytes 6 %, plasma cells 30 %, normoblasts 12 %, polychromic erythroblasts 5 %. — Thrombocytes 50,000.

Sternal puncture: Numerous highly immature plasma cells, many of which resembled reticular cells. — The plasma cells in the blood were of exactly the same type as those observed in the marrow sample.

Serum proteins: Total proteins 9.6 %, albumin 2.6 %, globulin 6.9 %.

Treated with transfusions, iron, and later, roentgen irradiation. Loss of weight and deterioration of the general health continued, but there was no pain.

Last blood examination (10 days before death): S. R. 170 mm/hour, Hb. 36 %, RBC 1,340,000, WBC 4,200; differential count: myelocytes 2 %, metamyelocytes 2 %, pol. neutro. 27 %, pol. eos. 1 %, lymphocytes 14 %, monocytes 12 %, plasma cells 18 %, erythroblasts 4 %.

The patient died at home about 18 months after the onset of the first clinical symptoms (no autopsy).

Case 3. 289/46 a man, aged 65, was admitted to the Medical Department A, Rigshospitalet, Copenhagen, on March 2, 1946. Death ensued on March 21, 1946.

For about 6 months prior to admission the patient had suffered from fatigue, poor appetite, and loss of weight; for about 5 weeks from stomatitis, and for about 4 weeks from frequent attacks of epistaxis. He was pale, sallow, and slightly cyanotic; the liver extended about 2 cm below the costal margin; the spleen could not be palpated; no enlargement of the lymph nodes. He had frequent attacks of epistaxis and complained of pain in the left side of the chest; there was tenderness of the third and fourth ribs and sciatic pain on the right side. The general health deteriorated rapidly, and death ensued 19 days after admission.

Bone roentgenograms: Nothing definitely abnormal.

Urine: Positive for albumin and Bence-Jones protein.

Blood examination: Blood urea 50—112 mg%; W. R. negative; S. R. 158—162 mm/hour, Hb. 55—45 %, RBC 2.25—2.00 million, WBC (on admission) 7,500, (on day of death: 16,000); differential count: pol. neutro. 7 %, band forms 3 %, lymphocytes

[1] The gamma peak is not of the normal type but has the form often seen in myeloma cases.

49 %, monocytes 1 %, plasma cells 40 % (on the day of death: 86 %). Thrombocytes 88,000.

Sternal puncture: 75 % more or less immature plasma cells.

Serum proteins: Total proteins 10.5 %, albumin 4.1 %, globulin 6.4 %.

Autopsy: Pneumonia of the upper lobe of the right lung. The spleen was slightly increased in size, but there was no enlargement of the liver or lymph nodes. — Microscopic examination showed massive diffuse plasma cell infiltration in the bone marrow, liver and spleen, slight plasma cell infiltration in the renal tissue but none in the lymph nodes, myocardium, or lungs.

Case 4. 1358/43 a man, aged 69, was admitted to the Medical Department (We are indebted to the head of the Medical Department, N. Chr. Gram, for permission to use the hospital record for the purpose of this publication) of the Military Hospital, Copenhagen, from November 6 to December 18, 1943: overstraining himself by lifting six months previously, the patient developed increasingly severe lumbar pain, which gradually radiated to the right leg; shortly before admission, pain in the chest also developed.

Physical examination revealed tenderness of the lumbar spine, right femur, and several ribs. — No enlargement of lymph nodes, liver or spleen.

Roentgen examination: Diffuse osteoporosis of the vertebral bodies of the thoracic and lumbar spine and osteolytic processes in the bodies of the ninth and eleventh thoracic vertebrae and in the body of the third lumbar vertebra. No abnormality of the skull.

Urine: Proteinuria, Esbach 1.5—5 ‰, and Bence-Jones proteinuria.

Blood urea: 43 mg%. — W. R. negative.

Blood examination: S. R. 137 mm/hour, Hb. 62 %; erythrocytes 2,780,000, total leukocyte count 8,780; differential count: pol. neutro. 31 %, eosinophils 6 %, lymphocytes 29 %, monocytes 8 %, plasma cells 26 % (typical, rather immature myeloma cells with nucleoli and with many transitional forms to elements resembling reticular cells). No immature granulocytes or erythroblasts.

Sternal puncture: 73 % plasma cells of the same type as that seen in the peripheral blood; 8 % reticular cells.

Serum proteins: Total proteins 9.1 %, albumin 3.5 %, globulin 5.6 %.

Roentgen treatment resulted in considerable relief of pain.

The blood was not examined during the last three months before death, which occurred in April 1944 about 12 months after the onset of the disease (no autopsy).

Comments and Review of Literature

Incidence: Plasma cell leukemia is, unquestionably, the rarest form of leukemia both in man and animals (35).

Statistical data concerning the incidence of plasma cell leukemia as compared, on the one hand, with that of aleukemic and subleukemic myelomatosis, and on the other, with that of other forms of leukemia do not appear to have been published previously.

During the period from January 1, 1943, to December 31, 1947, 193 cases of verified myelomatosis (multiple myeloma) in 107 men and 86 women, 6 solitary osseous myelomas in 4 men and 2 women, and 4 cases of plasma cell leukemia (the case published by SØEBORG-OHLSEN & NIELSEN (41) and our cases 2, 3 and 4) were notified to the Danish Cancer

Registry, which receives notifications from the whole country (population 4.1 million). (We are indebted to the director of the Danish Cancer Registry under the National Anti-Cancer League, JOHS. CLEMMESEN, for the statistical data.) During the same period 417 cases of myelogenous leukemia (214 men and 203 women) and 595 cases of lymphatic leukemia (379 men and 216 women) were notified.

In this material the ratio between non-leukemic myelomatosis and leukemic myelomatosis (plasma cell leukemia) is approximately 50 : 1, and the ratio between myelogenous + lymphatic leukemias and plasma cell leukemias is about 250 : 1.

According to the literature available in Denmark, it seems as if only 37 cases which may be designated as plasma cell leukemia have been reported. We have chosen — quite arbitrarily — only to record cases with at least 20 per cent plasma cells in the peripheral blood and have therefore excluded some cases listed in previous surveys (9, 23, 25, 27, 29); we have also rejected some previously published cases in which insufficient information was given.

The surveys presented below are based on the above-mentioned 37 cases from the literature + our own 4 cases.

Age and sex incidence: The age distribution of 39 of the 41 patients, in whom the age was stated, was as follows:

Under 30 years of age: 1, 30—39: 4, 40—49: 5, 50—59: 11, 60—69: 16, 70—79: 1, 80—89: 1. Youngest patient 25 years, oldest patient 80 years.

Neither sex seems to show a predisposition to plasma cell leukemia. Of 40 of the 41 patients in whom the sex was stated, 19 were men and 21 women.

Duration: In 34 of the 41 cases the duration was stated in the publications. Distribution according to duration from the onset of the first clinical symptoms to death was as follows:

Less than one month: 3, 1—3 months: 12, 4—6 months: 6, 7—12 months: 11, 18 months: 1, 24 months: 1 case. — The average duration of the 34 cases was 6 months. Most cases were thus either acute or subacute.

No distinct correlation seems to exist between the duration of the disease and the age of the patients.

Clinical manifestations: Clinically, the acute and subacute cases of plasma cell leukemia do not differ from other forms of acute and subacute leukemia. Lassitude, weakness, loss of weight and progressive anemia are the main symptoms, often combined with a hemorrhagic tendency, particularly from the nose and gingiva. Skin hemorrhages are fairly rare. Although there may be vague bone pain, this complaint is not very often encountered in the acute and subacute cases.

The cases of longer duration do not differ from the well-known symptomatology of cases of aleukemic myelomatosis. Pains in the bones is a predominant symptom.

Findings on physical examination: Enlargement of the liver was noted in 18 of 34 cases, enlargement of the spleen in 33 of 37 cases, and enlargement of lymph nodes in 17 of 26 cases.

Roentgen examination of the skeleton: Osteoporosis was noticed in 3 out of 28 cases examined and focal bone destruction in 15 cases. Thus, in a little more than one half of the cases examined, roentgen examination revealed bone lesions.

Blood findings: Moderate to severe hypochromic anemia is a constant finding, but even in the acute cases the anemia does not seem to be so pronounced as in other kinds of acute leukemia.

Distribution based on the maximum total leukocyte count for the 41 cases was as follows: 5—10,000 per cu.mm: 4, 11—20,000: 16, 21—40,000: 11, 41—60,000: 6, 61—80,000: 1, 81—100,000: 2, over 100,000: 1 (our case 1: 175,000).

Thus, 28 of the 41 cases had a total leukocyte count under 40,000 per cu.mm and the largest number of the cases were within the group 11—20,000. On the whole, the total count was much lower than in other forms of leukemia.

The total leukocyte count usually rises as the disease progresses and most of the maximum values stated are terminal findings. However, in four of the 41 cases a diminution of the total count was noted during the progression of the disease; in some of these cases roentgen treatment was given. When first seen, 11 of the 41 patients presented a normal total count (under 10,000).

There does not seem to be any convincing correlation between the duration of the disease and the total count.

As far as the terminal maximum values were concerned, the percentage of plasma cells in the peripheral blood varied between 20 per cent and 99 per cent, but only 17 of the 41 cases showed maximum values of more than 50 per cent, so that the number of leukemic cells in the peripheral blood is rather low as compared with that seen in other forms of leukemia. In almost all cases a distinct increase in the number of plasma cells in the peripheral blood occurred during the progression of the disease. When first seen, 10 of the 41 patients had less than 20 per cent plasma cells in the peripheral blood.

Judging from descriptions and illustrations, the cytology of the plasma cells in the peripheral blood seems in nearly all cases to exhibit the well-known morphological criteria for myeloma cells (2, 9), discriminating the latter form from normal bone marrow cells. A strikingly large

number of cases of plasma cell leukemia reveal markedly atypical and very immature myeloma cell types, so that it seems as if cases of myeloma with a slightly differentiated cell type have a stronger tendency to become leukemic than those with a highly differentiated cell type.

In other respects, the blood picture does not differ from that of aleukemic myeloma. Some immature granulocytes and a few erythroblasts are not infrequently observed, and a relative neutropenia may occasionally be seen.

Thrombopenia (most frequently with a thrombocyte count of about 50,000) is an almost constant finding in plasma cell leukemia.

Urine: Proteinuria and Bence-Jones proteinuria seem to occur with the same frequency in cases of leukemic and aleukemic myeloma.

Serum proteins: As regards serum protein changes plasma cell leukemia also seems to behave in the same way as myelomatosis. A pronounced increase in the sedimentation rate and hyperglobulinemia were noted in almost all the cases examined (1, 3, 14, 19, 21, 27, 29, 31, 32, 40, 43 + our own cases), but occasionally normal values (17, 25) or hypoproteinemia (10) were present. Electrophoretic patterns have been presented only in a minority of previously published cases of plasma cell leukemia. In one case of plasma cell leukemia, WUHRMANN & WUNDERLY (43) found a marked increase in the beta globulin, while LÜDIN (25) observed an increase in alpha and beta globulins but normal total globulins. Furthermore, WUHRMANN, WUNDERLY & HUGENTOBLER (44) stated — without further documentation — that plasma cell leukemia shows partly normal serum proteins and partly an increase in the alpha globulin. — In our case 1 an abnormal gamma globulin component, often encountered in myelomatosis, was observed.

Pathology: The occurrence of enlargement of the liver, spleen, and lymph nodes has already been mentioned under 'Findings on physical examination', and from the available data concerning the weight of the liver and spleen it is seen that the enlargement of the liver is only moderate, and in most cases this holds good also of the enlargement of the spleen. However, in three instances (6, 27, 29) the weight of the spleen ranged around 600 g, and in one instance (23) was 1,000 g.

Macroscopic bone foci largely correspond to those shown by roentgen examination.

Histological examination of material obtained by bone marrow puncture or at autopsy showed either a massive diffuse or both diffuse and focal infiltration of the bone marrow in all the cases examined.

Plasma cell infiltration of the liver was seen in all cases but one (25) and of the spleen in all cases but two (25, 34). Lymph node infiltration was noted in every case examined but two (25, own case 2), whereas kidney

infiltration was found in only 15 out of the 22 cases examined. Plasma cell infiltration of organs other than those already mentioned were observed in 11 of 13 cases examined; thus, infiltration of organs other than those commonly affected in leukemias seems to be rather common.

Treatment: As in other leukemias as well as in myelomatosis, roentgen treatment seems to be capable of reducing the number of leukemic cells in the peripheral blood and of relieving pain, although an effective therapy is unknown.

BAYRD & HALL (3) in one case observed an unusual remission after radiophosphorus therapy.

As plasma cell leukemia is such a rare disease, no experience has as yet been gained with regard to the effect of the various antileukemic and antineoplastic chemotherapeutic agents.

Discussion

The question whether plasma cell leukemia exists as a disease *sui generis* or merely represents a phase or extension of multiple myeloma has been discussed by many authors.

It is a well-known fact that cases of multiple myeloma not infrequently, notably in the terminal stage, reveal sparse to moderate numbers of atypical plasma cells (myeloma cells) in the peripheral blood. MORISETTE & WATKINS (28) found myeloma cells in the peripheral blood in not less than 41, or 73 per cent, of 56 patients with multiple myeloma (they did not state the number of plasma cells in the blood); BAYRD & HECK (4) observed plasma cells in the peripheral blood in 10 per cent of 83 patients, and GORMSEN (9) found 2—7 per cent plasma cells in the peripheral blood in 5 out of 20 patients with myelomatosis.

It is also well-known that cases of aleukemic multiple myeloma may occur without focal osseous lesions (diffuse myelomatosis of the bone marrow). Diffuse myeloma cell infiltration of the liver, spleen, lymph nodes, and other organs *without* or with only very few plasma cells in the peripheral blood is less frequent (24, 39, 42).

All transitional forms thus seem to exist between aleukemic, subleukemic, and leukemic myelomatosis with or without circumscribed bone foci and with or without infiltrations of other organs. It accordingly seems natural to regard cases of aleukemic, subleukemic, and leukemic myelomatosis as different manifestations of the same osseous plasma cell neoplasia (myelomatosis or multiple myeloma); even though some cases of acute or subacute myelomatosis may actually conform with the concept of leukemia, it seems more consistent to designate such cases as leukemic myelomatosis rather than plasma cell leukemia.

In contrast to this point of view, which is shared by such authors as PATEK & CASTLE (32) and BAYRD & HECK (4), RUBINSTEIN (37) prefers to regard all cases of myeloma as plasma cell leukemias. Biologically, cases of myeloma must unquestionably be considered to be of the same nature as those of leukemia, but as aleukemic myelomas are so predominant within the group, and as the designation myelomatosis has become sanctioned by use, the terminology suggested by other authors and by us seems to be more consistent than that proposed by RUBINSTEIN.

The question whether extramedullary »plasma cell leukemias» occur has recently been discussed by HECKNER (11), whose case, incidentally, does not seem to prove the existence of such a disease entity. However, from a purely theoretical point of view it does not seem unlikely that plasma cell leukemias might arise from lymphatic tissue and remain extramedullary, cf. cases of extramedullary lymphatic leukemia.

It seems now to be generally accepted that all cases of myeloma are plasma-cellular, and that bone marrow plasma cells, histogenetically, are derived from reticular cells.

The slight tendency which reticular cells and plasma cells have to appear in the peripheral blood in non-tumorous proliferations seems to be in good agreement with the fact that only very few cases of reticulosarcomatosis and myelomatosis are leukemic.

SUMMARY

Four cases of leukemic myelomatosis (»plasma cell leukemia») are reported.

From statistical data obtained from the Danish Cancer Registry the ratio between aleukemic + subleukemic myelomatosis and leukemic myelomatosis seems to be approximately 50 : 1 and the ratio between myelogenous + lymphatic leukemia and leukemic myelomatosis about 250 : 1.

The clinical manifestations, laboratory findings, and pathology of leukemic myelomatosis are discussed on the basis of 37 cases from the literature and the four cases reported. It is suggested that aleukemic, subleukemic, and leukemic myelomatosis should be regarded as different manifestations (or, perhaps, phases) of the same plasma cell neoplasia.

ZUSAMMENFASSUNG

4 Fälle von leukämischer Myelomatose (»plasma cell leukemia») werden geschildert.

Nach statistischen Ergebungen aus dem dänischen Krebsregister scheint das Verhältnis zwischen aleukämischer + subleukämischer Myelomatose und leukämischer Myelomatose etwa 50 : 1 zu sein und das Verhältnis zwischen myeloischer + lymphatischer Leukämie und leukämischer Myelomatose ungefähr 250 : 1.

Die klinischen Manifestationen, die Laboratorienbefunde und die Pathologie der leukämischen Myelomatose werden unter Zugrundelegung von 37 aus der Literatur gesammelten und 4 eigenen Fällen diskutiert. Es wird vorgeschlagen, die aleukämische, subleukämische und leukämische Myelomatose als verschiedene Manifestationen (oder vielleicht Phasen) der gleicher bösartigen Plasmazellenerkrankung zu betrachten.

RÉSUMÉ

Quatre cas de myélomatose leucémique (leucémie à plasmocytes) sont relatés.

Selon les données statistiques tirées du Registre Danois du Cancer la proportion entre les myélomatoses aleucémiques et subleucémiques d'une part, et les myélomatoses leucémiques d'autre part, est de 50 à 1; pendant que la proportion entre les leucémies myélogènes et lymphatiques d'une part, et la myélomatose leucémique d'autre part, est de l'ordre de 250 à 1.

Les manifestations cliniques, les résultats de laboratoire et l'anatomie pathologique de la myélomatose leucémique sont discutés à partir de 37 cas de la littérature et des 4 cas présents. Il est suggéré que les myélomatoses aleucémiques, subleucémiques et leucémiques devraient être considérées comme des manifestations diverses (ou peut-être des phases diverses) du même processus malin des plasmocytes.

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FROM THE RADIOLOGICAL CLINIC (DIRECTOR: PROF. CARL KREBS), UNIVERSITY OF AARHUS, DENMARK

PULMONARY ADENOMATOSIS (ALVEOLAR CELL TUMOR)

A Brief Survey and a Case Report

by

Olaf Brobeck

The vast majority of primary pulmonary tumors — the bronchial carcinomas — arise from the bronchial epithelium.

Reports during recent years have made it increasingly probable that the site of origin of such tumors may also be the alveolar cells. However, there has been a marked diversity of opinion as to the histogenesis and delimitation of these tumors; the justification for considering them as an entity has been questioned.

In recent literature, most investigators agree that the tumors arise from the alveolar epithelium, apparently often multicentrically; some express the view that it is a question of proliferating epithelium arising from the basal layer of the bronchial epithelium (HERBUT, 1946); others emphasize that mesenchymal cells of the alveolar septa may possibly be the site of origin (NEUBUERGER, 1941; NEUBUERGER & GEEVER, 1942).

Nomenclature and Delimitation. Alveolar cell tumor and pulmonary adenomatosis are the designations most frequently used. NEUBUERGER (1941) introduced the term 'alveolar cell tumor' as a neutral designation not signifying the ectodermal or mesenchymal origin of the cells. SWAN (1949) suggested that pulmonary adenomatosis (p. a.) should be reserved for pulmonary tumors which fulfil the following criteria: (1) alveolar cellular proliferation, characterized by the appearance of tall columnar mucus-producing epithelial cells; (2) absence of an intrinsic tumor of the bronchial tree, and (3) absence of a primary adenocarcinoma in any other part of the body.

Submitted for publication, Oct. 30, 1951.

Morphology. There are two macroscopic varieties:

(1) The multiple nodular: with white to greyish pink nodules, from miliary to marble size or larger, of a liver-like consistency, more or less evenly distributed in the lungs; this is the most common.

(2) The diffuse: involving from a single lobe of one lung to all lobes of both lungs. The cut surface shows a striking similarity to pneumonia in the grey hepatization stage.

The microscopic picture is the same in both forms. The alveoli are lined by non-ciliated or cuboidal cells frequently forming papillary protrusions into the alveoli. Sometimes, the cells are mucus-producing and may show varying degrees of anaplasia and hyperchromatism. Mitotic figures are rarely seen. The cells may lie as detached clusters in the alveolar spaces and the intact interalveolar septa may be thickened by fibrosis. The tumor may invade the lymphatics and spread to regional lymph nodes and possibly form metastases (remote lymph nodes, liver, brain and bones). The histological pictures of the metastases and primary tumor are identical. Approximately one half of the cases on record have shown some form of metastases. It has been doubted whether it is justifiable to classify the tumors forming metastases under the group of p. a. SWAN suggested the designation cancerous p. a. for these tumors.

Previous Reports. The first case of the nodular type of p. a. was reported in 1876 by MALASSEZ, the first of the diffuse type by MUSSER in 1903. In 1942, NEUBUERGER & GEEVER collected from the literature 25 cases which fulfilled the above-mentioned criteria for p. a. In summarizing the literature, SWAN (1949) stated that the number of cases on record was 61, including 9 of his own; since then at least 63 additional cases have been published.

Etiology. The etiology is unknown. In man the tumors, notably the benign variety, show a remarkable morphologic similarity to »jaagziekte» in sheep; most writers on the subject have given considerable attention to this condition. »Jaagziekte» is a fatal infectious pulmonary disease. The term »jaagziekte» refers to the peculiar watery sputum running from the mouth and nostrils of the animals after they have been driven some distance.

»Jaagziekte» occurs, inter alia, in Iceland, where the disease has been extensively studied by DUNGAL (1946), who expressed the view that the disease is possibly due to a virus. It may be transmitted from sheep to sheep but not to common laboratory animals; infection from animal to man has never been observed with certainty. A case of p. a. was recently reported from Montana, a state where »jaagziekte» is endemic; the patient had been in contact with diseased sheep prior to the development of symptoms (HILDEBRAND, 1948).

Attempts at transmission of p. a. by means of tissue from affected human beings to animals have proved unsuccessful (GOOD, MCDONALD, CLAGETT & GRIFFITH, 1950; DAVIS & SIMON, 1950). An infectious origin of human p. a. has not been proved to date.

Age and Sex Incidence. In 27 cases reported in the literature, SWAN found that the age ranged from 17 to 79 years with 74.1 per cent occurring in the 40—70 year age group. The cases seem to be equally distributed among men and women — a distribution which resembles that of bronchial adenoma, as opposed to the considerable male predominance of bronchial carcinoma.

Symptomatology. The most constant symptom is cough, at first dry or with only slight expectoration, in the later stages often productive of large amounts of clear, frothy sputum. Hemoptysis is not common, although the sputum may sometimes be blood-streaked.

Dyspnea is another conspicuous symptom. The lining of the alveoli with the characteristic epithelial cells reduces the respiratory surface of the lungs, and dyspnea on even the slightest movement is often a distressing symptom in the later stages.

Concurrent with the dyspnea there is often cyanosis and thoracic pain. Loss of weight and fatigue are common, while in most instances fever develops only in case of supervening pneumonia.

Prognosis. Pulmonary adenomatosis is usually a fatal disease. The patients die either of suffocation from progressive reduction of the respiratory epithelium, of pneumonia, or from metastases in other organs. Without treatment, death usually occurs in the course of a few months, but in exceptional cases the disease may be more protracted.

Treatment. The only effective treatment is surgical. Radiation therapy and treatment with nitrogen mustards have been attempted without any demonstrable benefit.

DELARUE & GRAHAM (1949) reported a case, apparently well, one year after pneumonectomy.

GOOD, MCDONALD, CLAGETT & GRIFFITH (1950) presented the results of operation in 8 patients; one was alive and symptom-free two years afterwards. Of 9 operated patients reported by SMITH, KNUDTSON & WATSON (1949), two were alive and free from recurrence five years after operation, which consisted in segmental resection and lobectomy, respectively; in each case the histological examination proved the condition to be benign.

So far, the number of operated cases is too small and the periods of observation too short for a final evaluation of the application of surgical measures, but in several of the cases a considerable palliative effect has been obtained; the patients have been relieved of the cough and expecto-

ration. Further experience will show if it is possible to obtain permanent cure or merely prolonged remission.

Diagnosis. The diagnosis is difficult to establish by ordinary clinical methods. Roentgen examination is of value in localizing the process and determining its extent, but the appearances are not characteristic. In its nodular form, it is impossible to differentiate p. a. from tuberculosis, sarcoidosis, fungus infections or pneumonoconiosis, and in the diffuse variety the roentgen diagnosis will most frequently be one of pneumonia or bronchial carcinoma.

Only by correlating the roentgenograms with the clinical findings, may a suspicion of p. a. be aroused, but a definite diagnosis can be established only by microscopic examination of tissue removed by exploratory thoracotomy.

Examination of the sputum may possibly give rise to a suspicion of a pulmonary tumor; occasionally, cells corresponding to those of the peculiar epithelial lining of the alveoli have been observed in the sputum.

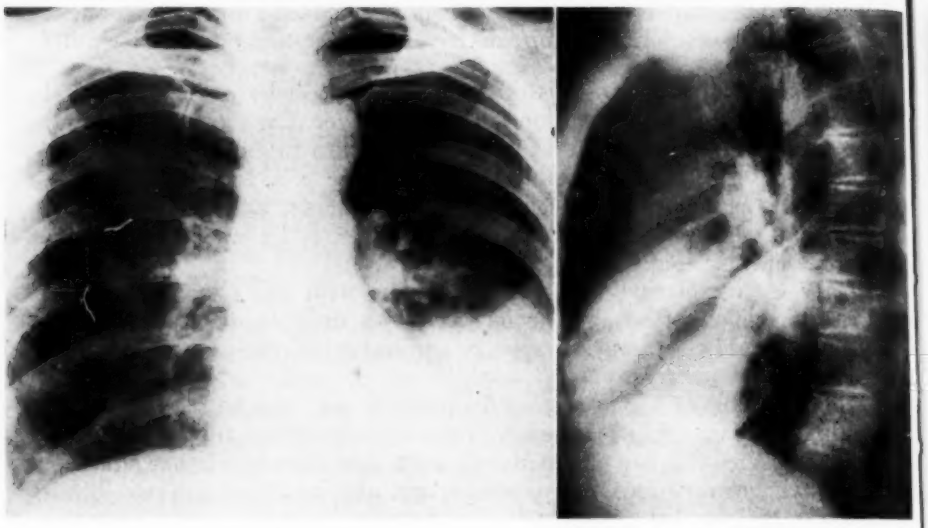
Bronchography does not provide any aid in the diagnosis; bronchoscopy will be helpful only if any bronchial secretion containing the characteristic cells can be aspirated.

Case report. The patient, a woman, aged 63, had had intermittent pain on the left side of the chest and a tendency to dyspnea for two months; she suddenly developed symptoms suggesting acute pneumonia and was admitted to hospital. After discharge, weakness and pain in the left chest recurred and increased, and two months later the patient was re-admitted to hospital. On examination, she had mild dyspnea, slight cyanosis of the lips and rales over the lower posterior part of the left lung.

Chest roentgenograms showed a massive density in the antero-inferior portion of the lower lobe of the left lung (figs. 1 a and 1 b); it was sharply demarcated anteriorly. In the left hilar region a pea-sized calcification was seen close to (behind) the bronchus of the left lower lobe. This was confirmed by planigraphy, which gave no additional information. *Bronchoscopy and bronchography* showed no signs of the presence of a tumor; the mucosa of the bronchi of the left lower lobe was red and swollen, and secretion was constantly produced from the lobe.

Repeated examinations of the sputum were negative for tubercle bacilli. No tumor cells were present in the aspirated pleural fluid or in the secretion from the lower-lobe bronchus. S. R. constantly increased (90—40 mm); Mantoux positive; W. R. negative. Other laboratory examinations: uncontributory.

During the stay in hospital: constant cough with mucoid sputum: fluctuating temperature with bouts exceeding 40° C. The patient was transferred to the University Surgical Clinic where left thoracotomy with lower lobectomy was performed. (Blixenkrone-Moller. I am indebted to Professor Blixenkrone-Moller for permission to make use of the description of the operation.) The lower lobe was united with the parietal pleura by numerous adhesions which were difficult to detach; when this had been done, it was seen that the entire lower lobe except for the apical part was the site of diffuse inflammation. The hilar region was edematous and infiltrated. The lower lobe was excised.



a. b.

Fig. 1. Massive density in inferior and anterior part of lower lobe of left lung.
a. Postero-anterior view. b. Lateral view.

The removed specimen contained three terminal ramifications of the main bronchus: they were found to be normal. The cut surface of the lobe was strongly suggestive of advanced pneumonia.

Microscopic Examination The normal structure of the pulmonary tissue was intact or was suggested by alveolus-like spaces, intercommunicating, and in places communicating, with slightly larger spaces (figs. 2 a and 2 b). However, a closer study revealed that all the alveoli were lined by columnar, slightly polymorphic epithelium of varying height. There were numerous papillary projections into the alveolar spaces. In some areas, remnants of original alveolar endothelium with tumor columnar epithelium below were seen. Thus, the microscopic picture conveyed the impression that the tumor tissue had grown into and actually lined the entire alveolar system. The tumor was mucus-producing as evidenced by the presence of mucus in the lumina and secretion in the cells. The epithelium was non-ciliated; a few mitotic figures were present.

No fibrosis of the connective tissue; no infiltrations in the alveolar spaces which here and there contained desquamated cell remnants; in some areas connective-tissue proliferation around vessels and lesser bronchi was observed. The tumor tissue lined the alveolar spaces and in places assumed a papillomatous, carcinomatous character (DALGAARD/LUND).

The postoperative course was uneventful. The patient was transferred to the Radium Centre, where she received rotation irradiation of the mediastinum (12,000 r). At repeated follow-up examinations she was comparatively well; the cough and expectoration had diminished and there was an increase in weight. However, chest roentgenograms showed progressive dissemination of small densities in both lungs (fig. 3).

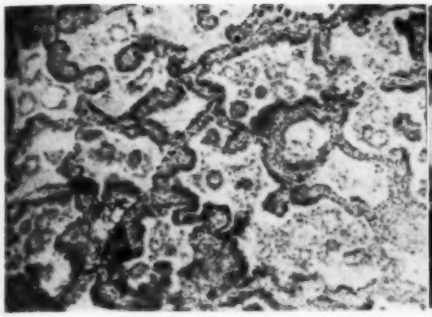


Fig. 2 a. Columnar epithelial cells lining alveolar spaces; cells show a tendency to form papillary projections into the alveoli.

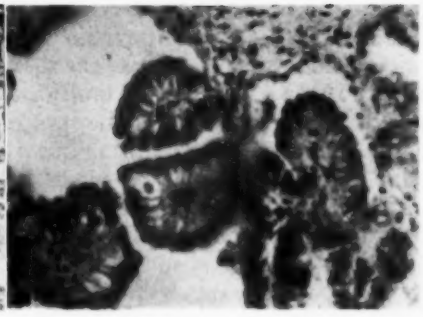


Fig. 2 b. Transition between flat alveolar cells and papillary infolded columnar epithelium.

Fig. 3. Dissemination in both lungs (18 months after Fig. 1).

Comments. Owing to the microscopic findings, the absence of an intrinsic tumor of the bronchial tree in the removed lobe and of a primary tumor elsewhere in the body, there appears to be justification in classifying the case as one of p. a. or alveolar cell tumor.

As in most previously reported cases, the correct diagnosis was not established until after histological examination of the affected pulmonary tissue.

Many investigators are inclined to the opinion that p. a. is of multicentric origin. In the case presented here, distinct signs of nodular dissem-

ination in both lungs developed after the removal of the apparently localized process. It is possible that this tumor also was of multicentric origin, although the first roentgenograms showed only a demarcated lesion. If the theory of the multicentricity of the tumor is correct, surgical intervention would seem inappropriate. However, several investigators point out that an operation may have a considerable palliative effect with improvement of the general health and relief of cough; this occurred in this case. It cannot be decided whether the roentgen therapy had a retarding effect on the further development of the condition. Experience gained in other cases so treated seems to show that p. a. does not respond to roentgen therapy.

SUMMARY

A brief survey of the pathology of pulmonary adenomatosis (alveolar cell tumor) is presented. The difficulty in establishing the diagnosis before histological examination of the pulmonary tissue has been carried out, is emphasized.

A case of a woman, in which microscopic examination of the removed pulmonary tissue showed changes characteristic of pulmonary adenomatosis, is reported.

ZUSAMMENFASSUNG

Ein kurzer Überblick über die Pathologie der Lungenadenomatosis wird gegeben. Die Schwierigkeit, vor der histologischen Untersuchung des Lungengewebes die Diagnose zu stellen, wird hervorgehoben. Ein Fall einer Frau, bei der die mikroskopische Untersuchung des entfernten Lungengewebes karakteristische Veränderungen der Lungenadenomatose zeigte, wird berichtet.

RÉSUMÉ

Un bref résumé de la pathologie de l'adénomatose pulmonaire (tumeur des cellules alvéolaires) est présenté. Il est précisé combien il est difficile d'établir le diagnostic avant que l'examen histologique du tissu pulmonaire n'ait été effectué.

Présentation du cas d'une femme chez qui l'examen microscopique du tissu pulmonaire prélevé révéla les altérations caractéristiques de l'adénomatose pulmonaire.

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FROM THE RADIOLOGICAL CLINIC (DIRECTOR: K. F. B. BUSCH), THE MUNICIPAL HOSPITAL, HORSENS, DENMARK.

ROENTGEN EXAMINATION IN COARCTATION OF THE AORTA

by

Fanny Busch

The clinical diagnosis of coarctation of the aorta is not difficult. The blood pressure in the upper extremities is elevated and lowered in the lower extremities, some-times to an inestimable degree. Other signs are those of extended collateral arterial circulation with 'stethoscopic changes' in the anterior and posterior thoracic walls and the presence of a heart murmur.

A roentgen examination of the chest shows typical notching at the inferior borders of the ribs. The form of the heart need not necessarily be changed, although a dilated left subclavian artery is usually seen.

TAUSSIG distinguished between two varieties of coarctation of the aorta, an infantile and an adult type. She described the infantile type as a diffuse narrowing from the point of issue of the left subclavian artery extending throughout the entire isthmus to the site where the ductus arteriosus Botalli inosculates, whereas in the »adult» type a localized stenosis of the aorta is present, usually slightly above the opening of the ductus arteriosus. In addition, she emphasized that other very significant malformations of the heart may be encountered in the infantile type.

Since the introduction of surgical treatment, consisting in resection of the narrowed aortic section, surgeons have raised several questions which can be further elucidated only by roentgen examination, *i. e.* the localization and the extent of the stenosis.

The ordinary roentgen examinations have therefore been supplemented in various ways, for example, by angiocardiography. However, after the intravenous injection of a contrast medium, a large portion is lost in the pulmonary vessels and the large collaterals, and the stenosis

Submitted for publication, Oct. 30, 1951.

Fig. 1. Boy, 13 years old, kymogram, indicating stenosis of aorta.

Fig. 2. Same patient. Planigram of the coarctation.

is reached by only a small quantity much diluted by the blood. Therefore, there are only slight prospects of obtaining a positive result by this method of examination.

In a different method, contrast medium is injected through a catheter passed up the cubital artery of the left arm up to the left subclavian artery. By this technique the contrast medium is injected just before the stenosis, and it gives clear roentgenograms and a good general view of the conditions of the stenosis.

Both methods are time-consuming and may even be dangerous. In several institutions in some countries, these methods are employed routinely, although, according to various publications, a mortality of about 1 per cent must be expected. Thus it would be preferable if the desired objective could be obtained without using these methods of examinations. It can scarcely be

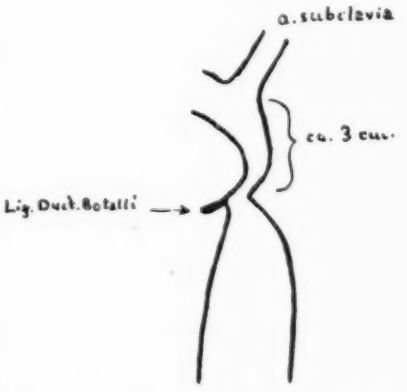

Fig. 3. Same patient. Outline of the operative finding.

doubted that by means of planigraphy and kymography it should be possible in a good many instances to obtain films showing both the narrow aortic section and its extent. In the kymogram it should also be possible to follow the course of the aortic arch by means of the typical pulsations.

Seven patients have been operated on for coarctation of the aorta in the Surgical Department of Horsens Municipal Hospital. In six of these patients the operation was successful. All the patients belonged to TAUSSIG's »adult» type (supposedly, patients of the infantile type will succumb before they reach the stage of being referred to operation).

Three of the patients were examined by means of intravenous contrast injections (Joduron 70 per cent, 40—50 ml), without success. In one of the patients, examination by means of the introduction of a catheter through the cubital artery was attempted. The catheter passed smoothly till it reached the common carotid artery where it was held up and the examination was interrupted.

The remaining three patients were examined by means of planigraphy and the site of the stenosis was definitely demonstrated. One of these patients, a 13-year-old boy, was also subjected to kymography, and the results of the previous examination were confirmed.

At operation it appeared that in the latter three cases; the stenosis corresponded closely with the roentgenographic findings.

SUMMARY

The author reviews briefly the methods of roentgen examination in coarctation of the aorta and suggests that in certain cases it should be possible to obtain the desired information from planigraphy and kymography. Three such cases are included.

ZUSAMMENFASSUNG

Die Verfasserin gibt einen kurzen Überblick über die Methoden der Röntgenuntersuchung bei der Coarctatio aortae und meint, dass es in gewissen Fällen möglich wäre, die gewünschten Informationen mit Hilfe der Planigraphie und der Kymographie zu erhalten. 3 derartige Fälle werden geschildert.

RÉSUMÉ

L'auteur passe brièvement en revue les méthodes d'examen radiologique dans le rétrécissement de l'isthme aortique et suggère que dans certains cas la tomographie et la kymographie seraient susceptibles de fournir les renseignements désirés; elle présente trois cas à l'appui de sa suggestion.

FROM THE RADIOLOGICAL CLINIC (DIRECTOR: K. F. B. BUSCH), THE MUNICIPAL HOSPITAL, HORSENS, DENMARK

ROENTGEN EXAMINATION IN PATIENTS WITH MITRAL STENOSIS BEFORE AND AFTER VALVULOTOMY

by

K. F. B. Busch

During the period from October 4, 1949, to June 19, 1951, operations for mitral stenosis were performed on 21 patients in the Surgical Department of Horsens Municipal Hospital. Of these patients, 17 underwent valvulotomy (Bailey's technique). All the operations were carried out by the Director of the Surgical Department, C. E. PRIP BUUS. Another patient with mitral stenosis on whom valvulotomy was performed by PRIP BUUS in Bergen Hospital, Norway, has also been included in the series, which thus consists of 22 cases.

Of the 18 patients who underwent valvulotomy, two died postoperatively of shock and pulmonary edema. Of the four patients on whom the operation was not completed, one died during the operation and another two days afterwards.

The objective of the examinations carried out in the Radiological Clinic was partly, to verify the diagnosis and to assist in the assessment of the general condition of the patients and partly, to attempt if possible to obtain information of value to the surgeon at operation.

During the postoperative period frequent bedside examinations were carried out, and eleven patients were subjected to one or more follow-up roentgen examinations.

The ordinary methods of roentgen examinations were employed. The heart was examined in the frontal and sagittal planes, at a focal distance of 1.5 m. Exposures were taken in the first and second anterior oblique positions, with contrast medium in the esophagus. Anteroposterior kymograms were taken of most of the patients with Strumph's kymograph. During the postoperative period ward examinations of the

Submitted for publication, Oct. 30, 1951.

patients were carried out by means of a portable roentgen unit at a focal distance of 1.20 m.

The size of the heart was estimated by a comparison of its maximum transverse diameter in the frontal plane with the width of the thorax at the level of the phrenicocostal sinus. All measurements were obtained by the same radiologist, which must be presumed to be important in order to obtain a sufficiently reliable assessment. The measurements proved to be adequate for the purpose and surprisingly constant in the numerous examinations of the individual patients.

Special attention was directed to the kymographic sections of the left side of the heart. The pulsations of the pulmonary artery and the left auricle and atrium were measured, since the size of these sections is of special interest to the surgeon. The size of the left auricle is of particular importance as, technically, valvulotomy can be successfully accomplished only if the auricle is large enough to enable the surgeon to introduce a finger with the mounted knife through the opened auricle into the atrium and there perform the operation.

In Anglo-Saxon literature, no distinction is made between the left atrium and left auricle; only the two terms »left auricle» and »auricular appendage» are used. However, in the following account I intend to use the two designations »left atrium» and »left auricle» to describe these sections of the heart.

The classical description of mitral stenosis is well-known. It speaks of the dilated left atrium forming the third cardiac curve on the left side, and of the left atrium projecting through the cardiac shadow to the right of the spinal column. The second left cardiac curve, formed by the pulmonary artery, is described as being slightly dilated. It is also stated that the left ventricle is not dilated.

The results of the examinations made in this clinic and the operative findings deviate to some extent from the classical description.

In almost all cases dilatation of the left ventricle was found; if it cannot be observed in the anteroposterior view, which is not always the case, it may be noted posteriorly in the second anterior oblique position. Only in three cases could we not demonstrate a dilated left ventricle. In 12 patients the right side of the heart was also dilated.

The third cardiac curve was found to be dilated in 15 patients, and in 19 patients the left atrium projected to the right of the spine. Only in one case could no dilatation of the left atrium be demonstrated.

The pulmonary arch on the left side was found to be dilated in 21 cases; only in one case was it impossible to demonstrate dilatation of the pulmonary artery. In addition, the views in the first anterior oblique position give some idea as to the size of the dilated conus pulmonalis, and in this respect, are often more useful than the frontal views.

The various sections of the left side of the heart were measured on the kymograms, but such measurements could not be directly compared with the operative findings, although they showed the dilatation of the pulmonary artery, and the atrium and auricle. On the other hand, kymographic examinations gave satisfactory information as to the presence of degenerative processes in the heart, notably atrial fibrillation and flutter, and there was complete agreement between the electrocardiographic and kymographic findings.

While, as already stated, the size of the pulmonary artery does not appear to be very impressive on the roentgenograms, the operative findings reveal quite a different picture. Again and again one is surprised at its enormous size; very often it is described as »twice the normal size» or »the thickness of a child's arm». Another finding which is frequently reported at operation is that the heart is rotated to the left, so that the left atrium lies posteriorly and the only structure which is seen on the left cardiac border is the highly blood-filled auricle. Thus, the possibility seems to exist that in mitral stenosis the third curve on the left cardiac border is formed by the left auricle and not, as generally assumed, by the left atrium. It may be supposed that the rotation is brought about by pressure exerted by the conus pulmonalis on the anterior thoracic wall; the heart rotated to the left, conceals its enlarged left ventricle, which, if it cannot otherwise be demonstrated, must then be sought for in the second anterior oblique position.

As part of the classical picture of mitral stenosis, the roentgen examination will in some patients also reveal a greater or smaller degree of pulmonary stasis (found in 13 of the 21 patients).

During the first few days after thoracotomy a small exudate appears on the left side of the chest in all cases and is accompanied by a dilatation of the heart; this dilatation is smaller on the left side than on the right. In 16 patients there was an average dilatation of the right side of the heart of 2.5 cm. This change, which, in my opinion, cannot be due either to the exudate or to fluid in the pericardium, soon recedes and often disappears completely before the discharge of the patient.

Of the patients subjected to valvulotomy, eleven were followed-up roentgenographically. The clinical findings need not be reported excepting to state that they proved disappointing. Instead of striking differences, the measurements of the cardiac shadow were practically unchanged. The form of the heart was also about the same, although there was no sign of a prominent auricle on the left cardiac border (it had been removed at the operation). The left atrium projected to the right of the spine as before and the size of the pulmonary artery also remained unchanged. The only new observation was that the pulmonary

stasis in practically all the operated patients had either completely disappeared or receded considerably.

Conclusions

Roentgen examinations were carried out on 22 patients with mitral stenosis admitted for operation. To the classical roentgenological description of mitral stenosis the following points may be added: (1) A dilated left ventricle will almost invariably be present; (2) the pulmonary artery is dilated to a considerably greater extent than would be expected from the roentgenogram. (3) The dilated pulmonary artery gives rise to a rotation of the heart to the left. This rotation overshadows the dilated left ventricle, and the left atrium is displaced dorsally, so that (4) the third curve on the left cardiac border in mitral stenosis must be presumed to be formed by the left auricle, which in the majority of cases is considerably enlarged. (5) The kymograms give good information as to the conditions of the left cardiac border, notably of atrial fibrillation and flutter. (6) During the immediate postoperative period the heart is somewhat dilated, but will soon return to normal size. (7) Post-operative follow-up roentgenograms show unchanged cardiac measurements, with the exception of differences due to the absence of the left auricle.

SUMMARY

The paper reviews the roentgen examination of 22 patients, on 18 of whom, valvulotomy was performed. 11 of the cases were also examined after operation. The appearances noted, it is claimed, varied somewhat from those classically described.

ZUSAMMENFASSUNG

Es wird ein Überblick über die Röntgenuntersuchungsresultate von 22 Patienten gegeben; bei 18 von diesen war Valvulotomie ausgeführt worden. Nach der Operation sind 11 dieser Fälle nochmals untersucht worden. Die erhobenen Befunde unterscheiden sich etwas von den klassisch beschriebenen.

RÉSUMÉ

Cet article passe en revue les examens radiologiques effectués sur 22 malades dont 18 subirent une valvulotomie. 11 de ces cas ont également été examinées après l'intervention. Les signes radiologiques différaient quelque peu de ceux qu'on décrit classiquement.

FROM THE DANISH CANCER REGISTRY UNDER THE NATIONAL ANTI-CANCER LEAGUE, COPENHAGEN, DENMARK

THE TOPOGRAPHICAL DISTRIBUTION OF LEUKEMIA AND HODGKIN'S DISEASE IN DENMARK 1942—46

by

Johannes Clemmesen, Th. Busk and *Arne Nielsen*

It happens now and again that the occurrence of leukemia or Hodgkin's lymphogranulomatosis suggests to the clinical worker that endemiologic studies should assist in the clarification of the etiology of these diseases. The material of The Danish Cancer Registry for the years 1942 to 1946 inclusive was therefore examined with a view to gauging the possibilities offered by this method of investigation, and the results analysed.

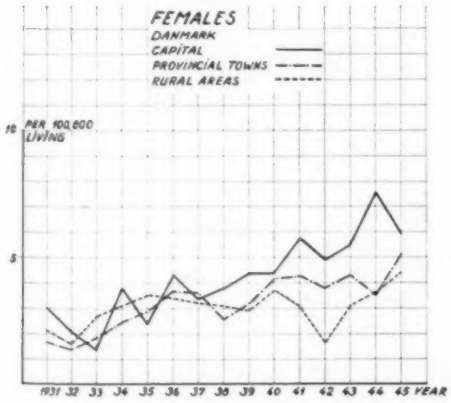

Diagram 1.

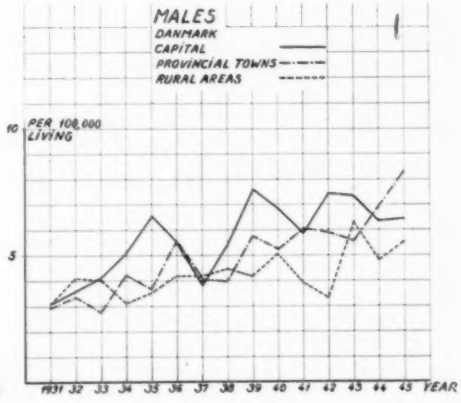

Diagram 2.

Diagram 1 and 2. Leukemia. Mortality rates in Denmark 1931—1945.

Aided by grants from The Anders Hasselbalch Leukemia Foundation.
Submitted for publication, Dec. 31, 1951.

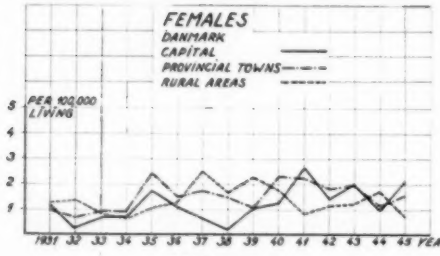

Diagram 3.

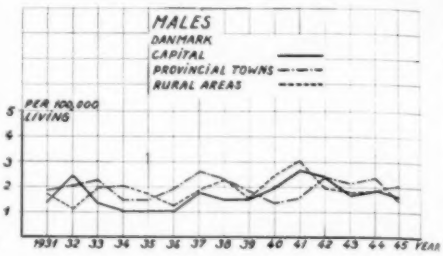

Diagram 4.

Diagram 3 and 4. Lymphogranulomatosis Hodgkin. Mortality rates in Denmark 1931—1945.

The material of »Cancerregisteret» is derived from notifications of all cases treated in hospital and of all autopsies. It is supplemented by all death certificates of cases of malignant disease, so that information is obtained in this way on cases treated in private practice. But the analysis presented here has been carried out separately for hospital cases since this group may be presumed to be diagnosed with more reliability than the former, which represents only a small fraction of the leukemia cases. Cases in which the diagnosis was made before 1942 have been tabulated separately.

In order to evaluate the stability of the occurrence of the diseases in question over a longer period, we have plotted the annual mortality rates, computed on the basis of the official mortality reports (Dodsaarsagerne for Kongeriget Danmark) in the above graphs.

Mortality

The graphs for Hodgkin's disease show constant values for both males and females, and a statistical evaluation has confirmed this impression. For all parts of the country the level of the curve for males is significantly higher than for females.

A study of the graphs giving the mortality rates for leukemia as a whole and the corresponding figures in table 1, will reveal a parallel increase in the mortality rate for leukemia in all parts of the country, with the exception that the increase for females in rural areas shows a less pronounced character than the rest of the material. The mortality for males is significantly higher than for females.

From a medical point of view, it seems not unlikely that the increase in leukemia observed through the period in question may be due to diagnostic improvements following the introduction of sternal marrow

Table 1. Mortality of Leukemia

Comparisons of trend and level

Groups compared		Slope		Level	
Sex	Area	value of t	degree of significance	value of t	degree of significance
M	C —PT	— 1.01	0	2.34	*
M	PT—RA	2.95	*	2.60	*
M	C —RA	1.47	0	4.42	***
F	C —PT	1.10	0	3.30	**
F	PT—RA	2.45	*	0.68	0
F	C —RA	3.15	**	3.56	**
M—F	C	— 1.38	0	4.56	***
M—F	PT	0.65	0	7.59	***
M—F	RA	0.48	0	4.70	***

The probability that the value of t is equal to or greater than the tabulated value is signified by

0	when the probability is	greater than 5 %
*	" " "	between 1 and 5 %
**	" " "	between 0.1 and 1 %
***	" " "	below 0.1 %

examinations etc. while the diagnosis of Hodgkin's disease presumably has been made under the same conditions as in earlier years.

Incidence

In order to give an impression of the topographical distribution in Denmark of leukemia and Hodgkin's lymphogranulomatosis, all cases have been plotted on maps according to the abode of the patient when first admitted to hospital.

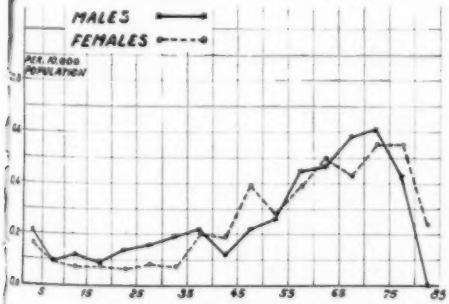

Diagram 5. Leukosis myeloica.

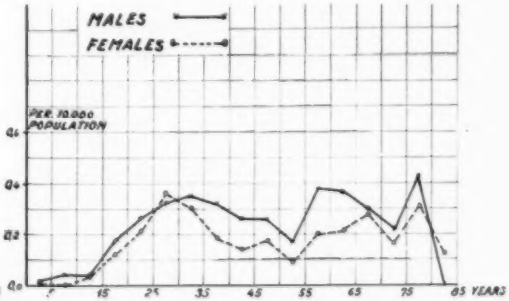

Diagram 6. Lymphogranulomatosis Hodgkin.

Diagram 5 and 6. Morbidity rates at various ages 1943—1947.

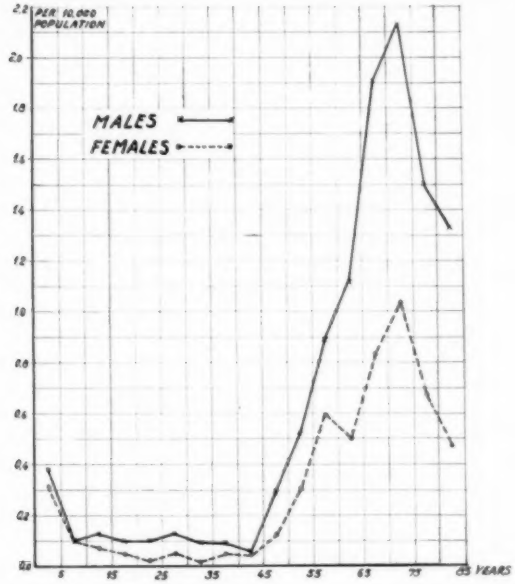

Diagram 7. Leukosis lymphatica. Morbidity rates at various ages 1943—1947.

The maps of the distribution of the two forms of leukemia showed no differences, and reproduction has therefore been omitted. The distribution of cases of Hodgkin's disease in Denmark for 1942—1946 is given in fig. 1 with special symbols for each year. It is striking that the Isle of Mors in Limfjord in the north-western part of Jutland shows a relatively high number of cases for the year 1942; the absence of cases in the south-eastern Isles of Moen and Falster is also noteworthy.

A statistical analysis was carried out in order to test whether any of the three diseases occur epidemically, and was based on the following considerations:

If the diseases occurred epidemically one would expect the number of cases to vary more from one year to another (which would not obtain if there were a constant risk of contracting the disease). We therefore compute the variation for each district and compare it with the variation one would expect if the risk of getting the disease were constant. In this case the number of patients must be distributed according to Poisson's formula, for which the best estimate of the variations is the mean of the numbers for the five years to be examined.

Table 2

The Danish Cancer Registry 1943—47.

Age	Mean population 1943—47	Lymphogranulomatosis (Hodgkin)			Leukemia myeloid			Leukemia lymphatic			Leukemia unspecified		
		Hosp. cases	Death certif. only	Total pr. 10,000	Hosp. cases	Death certif. only	Total pr. 10,000	Hosp. cases	Death certif. only	Total pr. 10,000	Hosp. cases	Death certif. only	Total pr. 10,000
Males													
0— 4	199,060	2	—	0.02	19	2	0.21	34	4	0.38	6	3	0.09
5— 9	160,500	1	2	0.04	7	—	0.09	7	1	0.10	3	—	0.04
10—14	150,540	3	—	0.04	9	—	0.12	10	—	0.13	4	1	0.07
15—19	154,400	13	—	0.17	7	—	0.09	8	—	0.10	2	—	0.03
20—24	162,220	20	1	0.26	11	—	0.14	8	—	0.10	3	2	0.06
25—29	157,960	24	1	0.32	12	1	0.16	10	—	0.13	3	1	0.05
30—34	160,160	27	1	0.35	14	1	0.19	7	—	0.09	3	—	0.04
35—39	153,940	22	3	0.32	16	1	0.22	7	—	0.09	3	1	0.05
40—44	138,820	18	—	0.26	8	—	0.12	4	—	0.06	1	—	0.01
45—49	124,440	14	2	0.26	14	—	0.22	17	1	0.29	1	2	0.05
50—54	107,740	6	3	0.17	13	1	0.26	27	1	0.52	2	1	0.06
55—59	94,160	15	3	0.38	20	1	0.45	38	4	0.89	1	1	0.04
60—64	80,640	12	3	0.37	18	1	0.47	42	3	1.12	6	2	0.20
65—69	65,820	9	1	0.30	18	1	0.58	56	7	1.91	2	—	0.06
70—74	45,980	4	1	0.22	13	1	0.61	47	2	2.13	4	3	0.30
75—79	28,000	5	1	0.43	4	2	0.43	18	3	1.50	2	5	0.50
80—84	13,500	—	—	—	—	—	—	8	1	1.33	—	1	0.15
85—	6,177	—	1	0.32	—	—	—	2	—	0.65	—	—	—
unstated	—	4	—	—	3	—	—	5	—	—	2	—	—
Females													
0— 4	190,740	—	1	0.01	12	3	0.16	28	2	0.31	4	4	0.08
5— 9	155,300	—	—	—	6	1	0.09	8	—	0.10	3	—	0.04
10—14	146,300	2	1	0.04	5	—	0.07	5	—	0.07	1	—	0.01
15—19	151,320	8	1	0.12	4	1	0.07	4	—	0.05	3	1	0.05
20—24	162,300	17	—	0.21	5	—	0.06	2	—	0.02	1	1	0.02
25—29	159,420	29	—	0.36	6	—	0.08	3	1	0.05	2	2	0.05
30—34	161,720	21	3	0.30	6	—	0.07	2	—	0.02	1	—	0.01
35—39	156,900	14	—	0.18	15	1	0.20	4	—	0.05	1	1	0.03
40—44	144,500	8	2	0.14	14	—	0.19	3	—	0.04	2	1	0.04
45—49	132,480	11	—	0.17	26	—	0.39	8	—	0.12	2	3	0.08
50—54	115,160	5	—	0.09	14	2	0.28	17	—	0.30	—	—	—
55—59	101,460	9	1	0.20	20	—	0.39	29	1	0.59	4	4	0.16
60—64	87,160	6	3	0.21	22	—	0.50	21	1	0.50	—	1	0.02
65—69	70,260	7	3	0.28	13	2	0.43	24	5	0.83	4	4	0.23
70—74	50,500	4	—	0.16	13	1	0.55	25	1	1.03	2	3	0.20
75—79	32,600	2	3	0.31	7	2	0.55	10	1	0.67	1	1	0.12
80—84	16,960	—	1	0.12	2	—	0.24	3	1	0.47	1	2	0.35
85—	8,142	2	—	0.49	—	—	—	2	—	0.49	—	—	—
unstated	—	2	—	—	—	—	—	4	—	—	1	—	—

The variance is computed from the formula:

$$\mathrm{MAK} = \frac{1}{4}\sum (X_r - X)^2$$

Fig. 1. Cases of Hodgkin's disease plotted according to the abode when first admitted to hospital.

where X_v is the number of cases in a single year and $\bar{X}$ is the mean for all five years. This variance divided by the mean will be approximately distributed as χ^2 with 4 degrees of freedom. Table 3 gives the result of the computations.

Table 3

The distribution of values of χ^2

Probability (per cent)	Corresponding percentiles of χ^2 for $f = 4$	Expected number of values of χ^2	Observed number of values of χ^2		
			Hodgkin	L. myeloid	L. lymphoid
0—10	—1.06	1.4	2	0	0
10—20	1.07—1.65	1.4	1	2	4
20—30	1.66—2.19	1.4	0	0	0
30—40	2.20—2.75	1.4	0	0	2
40—50	2.76—3.36	1.4	0	0	1
50—60	3.37—4.04	1.4	4	4	0
60—70	4.05—4.88	1.4	3	0	1
70—80	4.89—5.99	1.4	2	5	2
80—90	6.00—7.78	1.4	1	1	2
90—100	7.79	1.4	1[1]	2	2

[1] greater than 99.995 %.

It is seen that for Hodgkin's disease and myeloid leukemia there is a tendency towards greater values of χ^2 than expected from theory. The computations confirm the impression from the map since the value for Hodgkin's disease in County Thisted is very high and corresponds to a probability greater than 99.995 %; the numbers of cases amount to seven for 1942, 1 for 1943 and none for the following years; most of these patients were living in the Isle of Mors.

However, we do not find these variations sufficiently pronounced to be taken as evidence of an epidemical occurrence of Hodgkin's disease and myeloid leukemia, and for lymphatic leukemia the values of χ^2 are distributed according to expectation.

SUMMARY

A study of the topographical distribution of the incidence of leukoses and Hodgkin's disease in Denmark for the years 1942—1943 revealed no certain differences. During the years 1931—45 there was a gradual increase in the mortality rate for leukemia but not for Hodgkin's disease.

ZUSAMMENFASSUNG

Eine Untersuchung der topographischen Verteilung der Fälle von Leukosen und Hodgkinscher Krankheit in Dänemark während der Jahre 1942—1946 zeigte keine sicheren Unterschiede. Während der Jahre 1931—1945 fand man ein allmähliches Ansteigen der Mortalitätsziffern für Leukämien, jedoch nicht für die Hodgkinsche Krankheit.

RÉSUMÉ

Une étude de la répartition topographique des leucémies et des maladies de Hodgkin au Danemark durant les années 1942—1946 n'a révélé aucune différence prononcée. Pendant les années 1931—1945 il y a eu un accroissement progressif de la mortalité dans les cas de leucémie, mais non dans les cas de maladie de Hodgkin.

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FROM THE RADIOLOGICAL CLINIC (PROFESSOR CARL KREBS), THE DEPARTMENT OF EXPERIMENTAL CANCER RESEARCH (J. BICHEL) AND THE DEPARTMENT OF PATHOLOGY (PROSECTOR W. MUNCK), MUNICIPAL HOSPITAL AND UNIVERSITY OF AARHUS, DENMARK

SOLITARY PLASMOCYTOMA WITH TERMINAL DISSEMINATION

Three cases in the lumbar spine

by

Ena B. Dalgaard and *Jørgen B. Dalgaard*

Plasmocytoma is a rare, usually highly malignant, tumour composed of plasma cells, and is generally encountered as multiple osseous plasmocytoma or myelomatosis. Extramedullary solitary plasmocytoma, usually situated in the upper respiratory tract, has recently been described by P. E. ANDERSEN (1) and solitary plasmocytoma of the bone by BICHEL & KIRKETERP (4); these latter in 1938 reviewed all cases on record and stated that the term should be applied only to cases in which disseminated myelomatosis could be eliminated by roentgenographic, hematologic and pathologic investigations. Since then a few additional cases have been published (2, 5, 6, 7).

Three additional cases with lesions situated in the bodies of the lumbar vertebrae are now presented. The processes were at first localized but in the terminal phase of the disease other bones and organs became involved.

Report of Cases

Case 1 (891/45). — Male, aged 37, previously in good health, overstrained himself in October 1938, by lifting, had severe pain in the lumbar region, followed by periodic sciatic pain. In February 1941 a destructive lesion of L. 2 was interpreted as tuberculous spondylitis and treated with a plaster jacket and actinotherapy. In December 1941 osteosynthesis of the lumbar spine (Albee) was performed. In February 1945 recurring pain necessitated re-operation with bone transplantation; a small cavity with granulation tissue was found. Histologic diagnosis: Plasmocytoma (Fig. 1).

Aided by grants from the Lady Tata Memorial Trust, the Anders Hasselbalch Anti-Leucaemia Foundation and Shepler and Wife's Bequest, the Irma Foundation.

Submitted for publication Sept. 15, 1951.

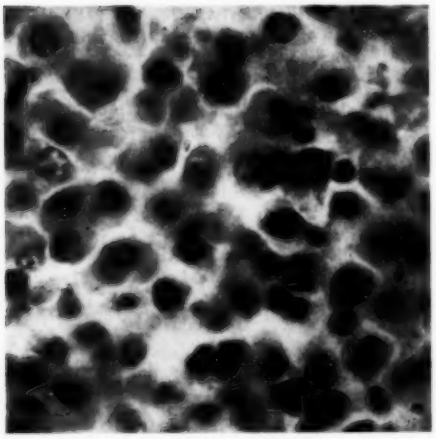


Fig. 1. Biopsy specimen from L. 2. The tumour is rich in large cells varying but mostly oval in shape and with abundant cytoplasm. The rounded nuclei are eccentrically placed and exhibit a chromatin distribution characteristic of plasma cells.

On admission to the Radium Centre, 1945, the patient was without pain and in good general health; weight 76 kg. Fixed lumbar kyphosis but no neurologic changes were found. Roentgen examination showed complete destruction of L. 2; no other bone changes. Laboratory findings: Hemoglobin level (Hb), red and white blood count (RBC and WBC), differential count (Diff.), sedimentation rate (S. R.) and serum proteins were all normal. No Bence-Jones protein in the urine. The sternal marrow was abundant in cells, but without abnormal forms. The patient was treated with roentgen, 1,500 r locally, with good response and was discharged; in October 1946 severe pain in the back radiating to both legs incapacitated him. Roentgen and laboratory examinations showed unchanged conditions and 1,000 r was given with fairly good results.

He was re-admitted in April 1947, bedridden owing to pain in the back and in poor general health. The destruction of L. 2 had progressed and invaded L. 3. A supportive corset was applied. In August his condition was still rather poor; body weight 71 kg; the Hb., RBC, WBC and Diff. as well as the S. R., formol-gel test and serum proteins all showed normal values (see Table 1); a roentgen examination of the spine showed practical unchanged conditions.

Thus up to Aug. 8, 1947 no signs of generalization had been disclosed.

However sternal marrow puncture revealed groups of typical myeloma cells on Aug. 11. The skull showed several small areas of rarefaction but all other bones examined were normal. Blood tests, including serum calcium, were still normal except the S. R. which was 15 mm (previously below 9 mm). 14 stilbamidine injections, totalling 2 g, were given with some relief of pain.

In October areas of rarefaction were found in the ribs. The S. R. was 29 mm increasing to 37 mm in January 1948, when the serum globulin was also definitely increased (Table 1); roentgen irradiation, 1,200 r, gave transient relief. In December some progression of the primary lesion could be detected and the Hb was 75 %, and RBC 3.7 mill.

Table 1

Serum protein determinations from Case 1

Date	May 1945	Aug. 1947	Jan. 1948	June 1948
Total proteins	7.4	6.3	7.6	7.6
Albumin	5.7	4.4	4.6	3.7
Globulin	1.7	1.9	3.0	3.9
Globulin percentage (normal 24—44)	23	30	40	51

Finally, lancinating pain all over the body occurred and the patient went downhill; the body weight decreased and the destruction progressed in the lumbar spine, skull and other bones. The S. R. increased to 117 mm and 126 mm (May 1948); serum calcium was 13 mg%, alkaline phosphatase 9 Buch units. The bone marrow contained typical myeloma cells and the serum globuline was 3.9 %. Bence-Jones reaction was weakly positive. The patient developed fever and died in June 1948.

The autopsy revealed an emaciated body weighing 52 kg with a marked hump caused by complete collapse and marked backward displacement of the first and second lumbar vertebrae; the cauda equina was compressed. In most of the vertebral bodies, in the femoral shafts, the sternum and the calvarium numerous rounded, jelly-like, greyish-black nodes, the size of a pea and larger, were present. Histologic examination of the bone marrow from L. 2 and the femur revealed numerous tumour-like clumps of oval myeloma cells with abundant basophilic cytoplasm and rounded eccentric nuclei of varying sizes with a chromatin arrangement like that of plasma cells, though coarser and irregularly distributed. Several large nuclei gave the cells a malignant appearance. No myeloma cells were seen in the congested spleen and liver or in the oedematous lungs.

Case 2 (4023/47). — Male, aged 40, factory worker, previously in good health, was admitted to the Neurosurgical Department in October 1947, suffering from periodic lumbar pain of 2 years' duration. It had lately been complicated by progressive muscular weakness of both legs. On examination, slight paresis of the knees, marked paresis of the ankles, paralysis of the toes as well as dysesthesia and hypesthesia from the knees to the feet with diminished reflexes was noted; Babinski's sign negative. Normal spinal fluid pressure and cell content, globulin 5—6 %, albumin 54 %, no tumour cells.

Roentgen examination revealed a tumour causing multilocular destruction of L. 5. Myelography and routine roentgenograms of the lungs, kidneys, stomach and colon were normal. On puncture of L. 5 a sparse punctate was obtained, containing numerous plasma cells, some of which were large with big, immature nuclei. A diagnosis of myeloma was made, and the patient transferred to the Radium Centre.

On admission he was weak and emaciated: the neurologic conditions were unchanged. The urine, Hb, S. R., RBC, WBC, Diff. as well as the serum calcium, phosphorus, acid phosphatase and sternal marrow were normal. Serum protein, Dec. 2 total: 6.6 %, albumin 4.3 %, globulin 2.3 %; (Jan. 6, 1948 — total: 5.7 %, albumin 4.1 %, globulin 1.6 %). During December the changes in L. 5 had involved the transverse processes, but there was no collapse of the vertebral body. Roentgen treatment, 1,200 r locally, improved the general condition, and the patient was discharged on Dec. 10.

On his way home he slipped and noticed a 'crack' in the back; he was re-admitted with complete paralysis of both lower extremities and collapse of L. 5. Laboratory tests were still normal. Roentgen rays (600 r), stilbamidine (2 g), and B-vitamin injections were given with some effect and he was discharged in February 1948 with good mobility of the hip and knee-joints but still suffering from severe pain and paralysis of both feet.

Re-admitted in May, essentially unchanged. Pentamidine therapy was instituted followed in October by massage and physiotherapy, and in February 1949 by the fitting of a plaster jacket. S. R. was then 4 mm.

In December 1949 he had severe pain in the back and legs, and paresthesia of the arms. The general condition was now poor and he had lost weight. The destruction of L. 5 had progressed and spread to L. 4. Hb. 75 %, RBC 3.8 mill., WBC 3,600, S. R. 32 mm. The urine was once positive for albumin but Bence-Jones protein was absent. The sternal marrow (Jan. 25, 1950) was still normal. However, an electrophoretic analysis (carried out by Niels Harboe, Elektroforeselaboratoriet, Copenhagen) of the blood on Jan. 12 revealed a γ-globulin of myeloma type (fig. 2). The patient went rapidly downhill and died on Feb. 16, 1950.

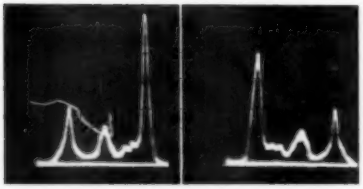
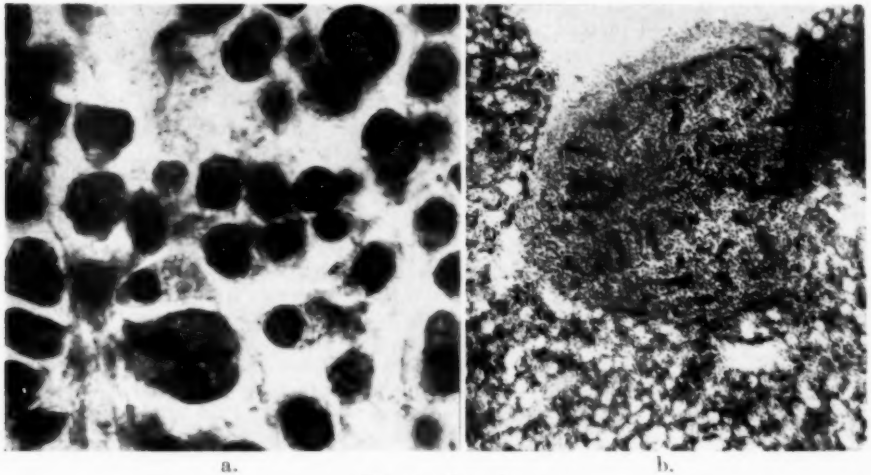


Fig. 2. Electrophoretic pattern of serum from Case 2 (Jan. 12, 1950) showing a distinct decrease in albumin; a_1 is slightly elevated; superimposed on the normal γ-globulin and inseparable from it is another γ-protein of myeloma type.

Autopsy: The body was emaciated. The lungs slightly oedematous. L. 5 had collapsed (1 cm in height) and was replaced by soft greyish tumour tissue, which had grown into L. 4 and the disc above it as well as backwards, compressing the cauda equina. Among numerous bones examined, only two ribs contained small greyish spots. Fresh smears and sections from the tumour in L. 5 showed a sparse and vascular stroma and numerous plasma cells, many of which were large and rich in basophilic cytoplasm that stained red with pyronine. The nuclei were eccentric and rounded with a patchy distribution of the chromatin and one or more distinct nucleoli. Several cells had two nuclei but mitoses were not seen (Fig. 3 a). In the humeral and femoral marrow, a thoracic vertebra and a lymph node near the tumour, a few myeloma cells and pyronine stainable (globulin) precipitates were present; a single small myeloma was found in the fifth left rib (Fig. 3 b). No myeloma cells were seen in the organs and no casts in the renal tubules.



a. b.

Fig. 3. Case 2.

a. Section from the tumour. Haematoxylin-eosin, approx. 1,000 ×.

b. Localized myeloma in a rib. Methyl green-pyronine 75 ×.

Case 3 (251/51). — Female, aged 71; 1939, cholecystitis; 1947, admitted to the Medical Department with hematemesis and melena. No ulcer was found, but the symptoms subsided after ulcer treatment; S. R. 13 mm.

In April 1950 lumbar pain, without history of trauma, spreading to the buttocks and the back of the legs. On readmission in June she was in fair nutritional condition

Fig. 4. Case 3. Pyelogram showing a tumour mass around the collapsed L. 3 dislocating the ureters.

(57 kg) but with a reduced and fixed lumbar lordosis and tense lumbar musculature: no tenderness along the sciatic nerve; Lasègue's sign negative; left patellar reflex absent; no definite Achilles tendon reflexes; sensibility normal.

Roentgen examination of the lumbar spine revealed some degree of spondylosis deformans and halisteresis. L. 3 showed severe destructive changes reducing the body to a third of its normal height and giving it an irregular spotted appearance resembling myeloma or metastases. The sacro-iliac joints, pelvis, colon and stomach appeared to be normal, but a roentgenogram of the lungs showed a raised left dome of the diaphragm. Urography (Sept. 7) showed normal renal filling, but lateral deviation of both ureters, particularly the left, suggesting a tumour mass around the collapsed L. 3 (Fig. 4).

Ordinary laboratory tests of urine (including Bence-Jones protein), feces and blood were normal except the S. R. which was 27 mm increasing to 43 mm during June and to 64 mm in July. The condition remained unchanged for some time, with attacks of pain of varying severity; rest in bed and short-wave therapy proved ineffective.

As the sternal marrow was found to be normal, puncture of L. 3 was performed on July 18. 3 ml of spontaneously coagulating blood was obtained. It contained some plasma cells, most of which were of the bone marrow type, while a few were distinctly larger with immature nuclei. In view of the roentgenographic findings these observations were considered as strongly suggestive of myeloma. So far no evidence of spread of the process had been disclosed. In September, however, numerous areas of rarefaction were observed on roentgen examination of the skull and a bone marrow puncture (iliac crest) showed numerous plasma cells of myeloma type, amounting to 18 per cent of the total cell count. The S. R. had increased: 92 mm on Aug. 9 and 126 mm on Sept. 2.

Roentgen treatment, 1,600 r locally, improved the condition, but in Jan. 1951 the patient suffered from constant severe pain in both legs, and she was transferred to the Radium Centre. She had lost weight (53 kg, later 51 kg), was pale but not critically ill. Lasègue's sign was positive on both sides at 70 degrees: the liver extended two finger-breadths below the costal margin.

Table 2

Serum protein determinations from case 2

With generalization a marked increase in the serum globulin occurred.

Date	March 1947	June 1950	Sept. 1950	Feb. 1951
Total proteins	6.4	6.4	7.0	9.2
Albumin	5.06	4.6	3.7	3.1
Globulin	1.35	1.8	3.3	6.1
Globulin percentage	22	28	47	66

Roentgen examination: further collapse of L. 3; the left half of the diaphragm still raised and extensive destruction now seen in the skull, two ribs, pelvis and both femora. The sternal marrow contained 10 per cent typical myeloma cells: blood examination now disclosed marked and progressive changes: Hb. 60 %—41 %, RBC. 3 mill.—1.8 mill., WBC 4,300—1,200, platelets 69,000—8,000; the S. R. increased steadily to enormous values: 144—164 mm. Serum globulin also increased (see Table 2), and electrophoresis showed a γ-globulin of myeloma type (Fig. 5). Serum phosphorus 6.6 mg%. The urine was negative for Bence-Jones protein on three occasions and positive on two.

Triethylene melamine therapy was instituted (total dosage 40 mg) with some relief of pain: the sternal marrow after treatment showed a paucity of cells with only a few

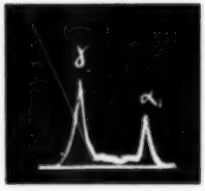


Fig. 5. Electrophoresis of serum from Case 3 showing similar findings as in Fig. 2: the abnormal γ-globulin peak is still more pronounced.

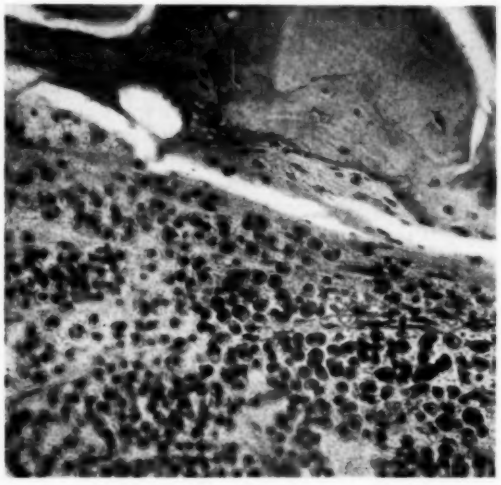


Fig. 6. Case 3. Section of the tumour from L 3 showing bone tissue and numerous typical myeloma cells.

plasma cells — it was not possible to see if cytologic changes were present and a differential count was impracticable. Finally fever supervened and the patient died on Feb. 19, 1951.

Autopsy. Body weight 51 kg; no hump or scoliosis. L. 3 had collapsed and was replaced by soft tumour tissue extending as a fist-sized mass to the left and a little to the right of the spine, displacing the left kidney and the spleen upwards and laterally. The tumour invaded the psoas muscle but not the adjacent discs, was red with brighter spots and of a crisp consistency. The rest of the spine was normal but in the calvarium numerous soft, rarefied areas were seen. Additional findings were: coronary sclerosis and myofibrosis, a small pleural exudate and small stones in the common bile duct. Histologic examination of the tumour tissue from L. 3 revealed numerous closely packed, large myeloma cells (Fig. 6). The spleen and femoral bone marrow also contained several myeloma cells; the liver and kidneys were normal.

Comments and Discussion

The localization of the primary myeloma to a single vertebra (L. 2, L. 5 and L. 3, respectively) and the histologic structure were identical in these three cases, and conformity is also found on a number of other points. The principal differences lie in the duration of the disease.

In all three cases the first symptom was periodic progressive lumbar pain radiating to the legs, commencing in Case 1 after trauma to the back. For 4 years this case was interpreted as tuberculous spondylitis and treated with immobilization until the correct diagnosis was made by biopsy during an osteoplastic operation. Case 2 was referred to the Neurosurgical Department owing to the neuralgiform pain caused by the pressure of the tumour on the cauda equina, while Case 3 was admitted to the Medical Department for sciatica.

In all cases the roentgen examination was suggestive of a tumour (in Case 3 a myeloma was actually mentioned) but the correct diagnosis ultimately was made by biopsy. The importance of this diagnostic aid must therefore be strongly emphasized.

Biopsy was carried out as an aspiration puncture of the vertebral body to a depth of 9 cm under local anaesthesia with roentgen control, 7 cm laterally to the midline at an angle of 45 degrees forwards and medially.

In all three cases two distinct phases of the disease can be recognized — before and after generalization.

Before generalization, exclusively local symptoms were present. Although these might be incapacitating, with severe pain and neurological complications due to pressure on the cauda equina or nerve roots, the general condition of the patients remained unaffected and the blood chemistry was normal. In this phase the lesion is amenable to roentgen treatment which in our cases gave some relief and improvement of general health.

Duration of this phase: In Case 1 not less than 9 years (to Aug. 1947), *i. e.* 2 years after the histologic diagnosis; in Case 2 about $4^1/_2$ years (to Dec. 1949), *i. e.* $2^1/_2$ years after histologic diagnosis; in Case 3 about 5 months (to Sept. 1950), *i. e.* 3 months after histologic diagnosis.

Owing to incorrect diagnosis the first patient did not receive roentgen treatment for 7 years, and the second patient was not treated during the first 2 years, while the early diagnosis in the third case permitted adequate roentgen treatment 4 months after the onset of symptoms. Nevertheless, the first two patients, who were young, survived for another 3 years, whereas the third, elderly patient, died 6 months after the institution of roentgen therapy.

During the first phase of the disease, all three patients may reasonably be designated as cases of solitary plasmocytoma with due regard to the strict requirements of BICHEL & KIRKETERP (4), as all were subjected to careful roentgenologic, hematologic and chemical examinations (including bone marrow biopsy).

After generalization: In the terminal phase of the disease, and notably at autopsy, definite signs of dissemination were found in all three patients. Actually, to establish this only one definite criterion is needed, *i. e.* the presence of myeloma cells in the sternal marrow, roentgenologic demonstration of dissemination or an increase in the serum globulin, most simply observable as a marked increase in the sedimentation rate and a positive formol-gel reaction. However, it is a striking fact that generalization manifests itself in these different ways almost simultaneously and at the same time a marked deterioration of the general condition supervenes.

In Case 1 myeloma cells were demonstrated in the sternal marrow in Aug. 1947, and at the same time definite roentgen signs of dissemination to the calvarium were observed after numerous negative examinations of various bones; increase in the S. R. and globulin occurred in Oct. 1947 and Jan. 1948 respectively.

In Case 2 the number of examinations during the last admission was less because the patient was very ill and objected to the taking of blood samples. In Dec. 1949 the condition was poor, the S. R. 26 mm but the sternal marrow normal. The only definite sign of dissemination obtained before autopsy in this case was the electrophoretic findings (γ-globulin of myeloma type).

In Case 3 dissemination was indicated (Sept. 1950) by roentgen examination of the skull, bone marrow aspiration and increase in the serum globulin. By then the S. R. had for some time shown a tendency to increase.

All three patients died with typical signs of myelomatosis, in poor general condition, emaciated, severely anaemic and in great pain.

The results obtained by treatment with diamidines have recently been reported by BICHEL (3) in whose case reports the first two of these patients were included.

The autopsy findings were dominated by the primary tumour, anaemia of the organs, hyperplasia of the bone marrow, and in two cases, visible myelomas in the skeletal system. The microscopic appearances were uniform and typical of malignant plasma cell myeloma.

The question whether multiple myeloma (myelomatosis) usually, or perhaps always, begins as a solitary myeloma (plasmocytoma) and metastasizes through the bone marrow system, is not a new one and obviously cannot be solved by these three cases which, after the lapse of 9 years, 4½ years and 6 months respectively, passed from the stage of distinct solitary plasmocytomata into cases of myelomatosis. However, it may be supposed that also other cases of myelomatosis with initial lumbar and sciatic pain may originally have been solitary lesions not diagnosed at that phase of the disease. More frequent use of biopsy of the affected vertebra may result in disclosure of other cases similar to those reported here.

SUMMARY

A diagnosis of solitary plasmocytoma should be confined to microscopically verified cases in which chemical, hematologic and roentgenographic examinations fail to show evidence of myelomatosis. Three such cases with localization of the tumour to a lumbar vertebra are reported.

Two separate phases may be distinguished in this condition: the solitary plasmocytoma and the generalized stage. Dissemination may be disclosed by the striking increase in the S. R. and serum globulin (detectable chemically or electrophoretically), a positive Bence-Jones reaction; the occurrence of myeloma cells in the bone marrow; areas of rarefaction in various bones and aggravation of the general condition.

The findings support the view that myelomatosis often commences as a solitary plasmocytoma and metastasizes through the bone marrow system.

ZUSAMMENFASSUNG

Die Diagnose eines solitären Plasmocytomes sollte auf mikroskopisch verifierte Fälle beschränkt sein, in denen die chemische, hämatologische und röntgenologische Untersuchung nicht das Vorhandensein einer Myelomatose nachweisen kann. Drei derartige Fälle mit dem Tumor in einem Lumbalwirbel werden berichtet.

Zwei besondere Phasen sollten bei der Erkrankung unterschieden werden: das solitäre Plasmocytom und das generalisierte Stadium. Generalisierung kann durch das auffallende Ansteigen der Senkungsreaktion und der Serumglobuline (nachweisbar auf chemischem oder elektrophoretischem Wege) sowie durch Nachweis des Bence-Jonesschen Eiweisskörpers im Harn entdeckt werden; weiterhin durch das Vorkommen von Myelomzellen im Knochenmark, durch rarefizierte Gebiete in verschiedenen Skeletteilen und durch Verschlechterung des Allgemeinzustandes.

Die erhobenen Befunde unterstützen die Ansicht, dass die Myelomatose oft als solitäres Plasmocytom beginnt und dann durch das Knochenmarksystem metastasiert.

RÉSUMÉ

Le diagnostic de plasmocytome solitaire devrait être limité aux cas microscopiquement vérifiés dans lesquels les examens chimiques, hématologiques et radiographiques ne peuvent déceler aucune myélomatose. Trois cas de cette espèce, présentant une localisation de la tumeur au niveau d'une vertèbre lombaire, sont décrits.

Il est utile de séparer les deux phases suivantes: le plasmocytome solitaire et la période généralisée. La dissémination peut être révélée par l'augmentation considérable de la sédimentation (S. R.) et de la globuline du sérum (décelée chimiquement ou par électrophorèse), par la réaction de Bence-Jones positive, par la présence de cellules myélomateuses dans la moelle osseuse, par des aires de raréfaction dans divers os et par l'aggravation de l'état général.

Ces données incitent à penser que la myélomatose débute souvent par un plasmocytome solitaire et que celui-ci est suivi d'une métastase affectant le systéme médullaire des os.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: ERIK EBBEHØJ), TOWN AND COUNTY HOSPITAL, KOLDING, DENMARK.

THE SAFETY FACTOR IN ULTRASOFT ROENTGEN IRRADIATION

by

Erik Ebbehøj

When the skin has been damaged, either by trauma, chemical or thermic action, or excessive radiation, it shows marked regenerative powers, if only its nutrition has not been impaired. We do not know exactly at what depth in the skin radiation damage, resulting in radionecrosis or appreciable contraction of scar tissue, occurs. The depth must vary with the thickness of the skin and its blood supply. The untoward effects are probably a combination of injuries occurring at a depth of 3—8 mm. In order that we should not be too optimistic about the harmlessness of ultrasoft roentgen rays, let us assume here that the damage which results in radionecrosis occurs at a depth of about 3 mm, leaving out of account the superficial papillary atrophy which merely is represented by an area of slightly glossy skin. It is the radionecrosis which constitutes the real risk and gives rise to concern.

From table 1 the dose at a depth of 3 mm with various qualities of radiation is obtained and hence it may be calculated how large the *surface dose* of a certain quality of ultrasoft radiation should be, in order to obtain the same effect at a depth of 3 mm.

However, these figures are only of secondary interest in this connection; the effect in dermatological radiation therapy is not aimed at the dead, keratinized superficial cells of the epidermis but at the tissues situated at a depth from 0.3 mm to about 2 mm from the surface. In most skin lesions in which radiation therapy is used, the affected layers have a thickness of, or may by means of scraping or compression be reduced to, 2 mm or less.

Submitted for publication Oct. 31, 1951.

Table 1

Quality	1	2	3	4	5	6	7	8	9	10
H. V. L., mm skin	0.12	0.26	0.34	0.7	1.15	1.6	Ph. I	4.65	Ph. II	130 kv.
Depth 0 mm, r	100	100	100	100	100	100	100	100	100	100
» 0.3 »	18	43	54	71	80	85	94	95	97	100
» 1 »	2.9	10	17	39	54.5	62.5	83	83.5	90	99.5
» 2 »	0.9	2.2	7	22	36	44	70	71.5	82.5	99
» 3 »	0.0037	0.67	2.5	13	25	32	60.5	62	75	98.5
» 4 »	0.0002	0.27	1.5	9.4	18.5	24.6	51	54	69	98
» 5 »	0.00001	0.12	0.99	6.4	14.5	20.4	44.5	47.5	62	97.5

Distribution of various qualities of radiation for each of the uppermost 5 mm of tissue.

1. produced by Bucky tube at 6 kv. ..... H. V. L. 0.12 mm skin
2. » » » » » 9 » ..... » 0.26 » »
3. » » » » » 12 » ..... » 0.34 » »
4. » » Machlett A. E. G. 50 at 20 kv. ..... » 0.72 » »
5. » » » » » 20 », filter 0.1 mm Al ..... » 1.15 » »
6. » » » » » 30 », » 0.2 » » ..... » 1.60 » »
8. » » » » » 50 », » 0.5 » » ..... » 4.65 » »

(The Bucky tube was provided with a Lindemann window and the Machlett A. E. G. 50 with a beryllium window.)

7. Ph. I and 9. Ph. II are the most superficial qualities which can be obtained from Philips contact roentgen unit (VAN DER PLAATS 1938: Behandeling van Huid Carcinomen met Roentgenbestrahling volgens de Roentgenkaustiekmetode). The quality Ph. II corresponds very closely to the most superficial radiation produced by Siemens Monopan unit.

10. 130 kv. rays produced with a roentgen tube without a special window and provided with an extra filter of 3 mm Al. This radiation passes through the first 5 mm of tissue almost without any decrease in intensity.

Let us first consider the safety factor when the objective is to administer a certain dose at a depth of 0.3 mm.

Table 2

	100 r at a depth of 0.3 mm									
H. V. L., mm skin	0.12	0.26	0.34	0.70	1.15	1.60	Ph. I	4.65	Ph. II	130 kv.
Depth 3 mm, r	0.02	1.55	4.5	18	31	38	64	65	77	98.5
Factor	4,925	63	21	5.5	3.2	2.6	1.54	1.52	1.27	1

Table 2 shows the number of roentgen units administered at a depth of 3 mm when a dose of 100 r of varying quality is placed at a depth of 0.3 mm. Let us imagine that for a radiation of 130 kv quality, filtered by 3 mm Al, we have determined the largest dose at a depth of 0.3 mm which just does not produce permanent radiation damage — we may call it the maximum dose at a depth of 0.3 mm and fix it at 1. It appears from the table that the softer radiation gives a larger maximum dose at a depth of 0.3 mm than the harder radiation. For example, with quality Ph. II we can give 27 per cent more at a depth of 0.3 mm; with quality H. V. L. 0.34 mm skin, 21 times as much, and with quality

H. V. L. 0.12 mm skin, approximately 5,000 times as much as with the 130 kv quality of radiation.

The proportionate numbers of the table give an indication of the size of the safety factor when a dose at a depth of 0.3 mm is administered.

The softer the quality of the radiation — the greater the safety factor, the greater the difference between the therapeutic dose and the maximum dose and the wider the range of the therapeutic effect.

The figures show that it is not a question of small doubtful variations. The safety factor is large especially when working in the actual grenz ray range with a H. V. L. of less than 0.4 mm skin. If we place the distribution figures for radiation produced by voltages ranging between 60 kv and 120 kv — which are still used in dermatological radiation therapy in many institutions — they will all lie in the columns for Ph. II and 130 kv, *i. e.*, the maximum doses for these qualities of radiation at a depth of 0.3 mm are all less than 27 per cent higher than the maximum dose for 130 kv; this in turn means that a reduction of the voltage from 130 kv to 50 kv does not result in any decrease in the danger of radiation damage in dermatologic therapy. On the other hand, if we use a ray quality with a H. V. L. of 0.34 mm skin, we may give 21 times as large a quantity of roentgen at a depth of 0.3 mm as with 130 kv, before we run the same risk of radiation damage; this is a very significant reduction of the risk.

Let us next examine the size of the safety factor when a subject receives treatment at a depth of 1 mm.

Table 3

	100 r at a depth of 1 mm									
H. V. L., mm skin	0.12	0.26	0.34	0.70	1.15	1.60	Ph. I	4.65	Ph. II	130 kv.
Depth 3 mm, r	0.12	6.3	15	33	45.7	52	71	74	83	99
Factor.....	825	15.5	6.6	3	2.15	1.9	1.4	1.33	1.19	1

Table 3 shows the number of r units at a depth of 3 mm when doses of 100 r at a depth of 1 mm with different qualities of radiation are given, together with the pertinent safety factors. With decreasing H. V. L. an increase occurs in the range of therapeutic effect, although it is distinctly less than at a depth of 0.3 mm.

In the usual radiation therapy of eczemas and similar superficial skin affections, an endeavour is made to obtain an effect at a depth of 0.3 —1 mm. Thus, the safety factor for the various qualities of radiation will lie between the values stated in tables 2 and 3. For example, the safety factor for radiation with a H. V. L. of 0.34 mm skin lies between 6.6 and 21 and for H. V. L. 0.26 mm skin between 15.5 and 63; this

means that it is possible to apply a sufficient therapeutic dose to this layer of the skin with these types of radiation without any risk of radiation damage.

How does the safety factor affect treatment at a depth of 2 mm?

Table 4

	100 r at a depth of 2 mm									
H. V. L., mm skin	0.12	0.26	0.34	0.70	1.15	1.60	Ph. I	4.65	Ph. II	130 kv.
Depth 3 mm, r	4	30	36	62	71	74	86	86	93	99.5
Factor.....	25	3.8	2.75	1.6	1.4	1.35	1.15	1.15	1.07	1

Table 4 shows the number of r units at a depth of 3 mm in the tissue when doses of 100 r at depth of 2 mm are given and the calculated safety factors for the various qualities of radiation. Further, at this depth, the difference between the therapeutic dose and the maximum dose — the range of therapeutic effect — or the safety factor — increases with the softness of the rays, even though the figures are much smaller than those for doses at depths of 1 mm and 0.3 mm.

If we place the qualities of radiation produced at voltages from 50 to 130 kv in tables 3 and 4, they will all fall between the values for Ph. II and 130 kv, *i. e.*, their maximum dose at a depth of 1 mm will be less than 19 per cent and at 2 mm less than 7 per cent higher than for 130 kv filtered with 3 mm Al. This in turn means that the risk of radionecrosis is practically the same whether we use 130, 100, or 50 kv for doses at a depth of 1—2 mm. Furthermore, it may be seen from these tables that the range of qualities produced by contact roentgen tubes do not constitute a safety factor of much practical importance, as they give an increase in the maximum dose of less than 15 per cent at a depth of 2 mm.

On the other hand, it will be seen that if a quality with a H. V. L. of 1.60 mm skin is used, it is possible at a depth of 1 mm to give 90 per cent more and at a depth of 2 mm, 35 per cent more, before there is the same risk of radionecrosis as when using a quality which passes through the skin with practically no decrease in intensity.

If an epithelioma of a thickness of 1 mm is to be treated, and ordinary soft roentgen rays or qualities of roentgen rays obtained from contact tubes are used, healing without radionecrosis depends exclusively on the difference between the cancer dose and the skin necrosis dose. If, on the other hand, ultrasoft rays with a H. V. L. of 1.60 mm skin are employed, there is a safety margin of 90 per cent, and if a quality with a H. V. L. of 0.34 mm skin is utilised, more than six times the cancer dose may

be administered before the risk of radionecrosis is the same as in the case of 130 kv.

If the radiation damage which gives rise to radionecrosis occurs at a greater depth than we have assumed — 3 mm — the radiation produced by contact roentgen tubes at 60—100 kv will show an increased safety factor as compared with the rays produced at 130 kv, but at the same time the safety factor for qualities with a H. V. L. of 1.6 mm skin or less will increase enormously. The latter possibility provides additional evidence in favour of the use of ultrasoft roentgen radiation in superficial therapy.

Ultrasoft roentgen rays are not so dangerous in dermatologic therapy as other roentgen rays; when using ultrasoft rays, the operator need not reduce his requirements as to the size of the dose for fear of radionecrosis.

SUMMARY

The risk of radionecrosis is almost the same whether radiation produced at 130 kv, 60 kv, or from contact roentgen tubes be employed. On the other hand, the risk is reduced by using ultrasoft roentgen rays.

The softer the quality of the ultrasoft rays — the smaller the risk of radionecrosis, the wider the range of therapeutic effect and the greater the safety factor.

ZUSAMMENFASSUNG

Das Risiko einer Röntgennekrose bleibt nahezu dasselbe, ob man nun 130 kV, 60 kV oder die Qualitäten der Nahbestrahlungsapparate benutzt. Dagegen wird es durch Verwendung ultraweicher Röntgenstrahlen herabgesetzt. Je weicher die verwendete ultraweiche Strahlung ist, je geringer ist die Gefahr einer Röntgennekrose und um so grösser ist die therapeutische Wirkungsbreite sowie der Sicherheitsfaktor.

RÉSUMÉ

Le danger de radionécrose est sensiblement le même après radiothérapie sous 130 à 60 kv et après radiothérapie de contact. Le danger est moindre si on emploie les rayons de Bucky. Plus les rayons sont mous, moins il y a de risques de radionécrose, plus grand est l'effet thérapeutique et plus grande est la marge de sécurité.

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: J. FRIMANN-DAHL), ULLEVÅL HOSPITAL, OSLO, NORWAY

EXAMINATION OF THE SOFT TISSUES OF THE CHEST

By

J. Frimann-Dahl

Pathological changes in the soft tissues of the extremities and the flanks have been thoroughly studied by various authors. LAURELL, in 1928 described the abnormal structures visible in the subcutaneous tissues in early stages of osteomyelitis; similar changes were observed in the flanks in peritonitis. SKARBY, in 1946 stressed the importance of a careful investigation of the soft tissues of the flanks in cases of perirenal inflammations. CARTY and FRANZELL investigated the soft tissues in a variety of lesions of the lower extremities, and FRIMANN-DAHL used the method in 1949 for the diagnosis of acute thrombosis.

However, in lesions of the chest, such investigations have been of secondary importance and only occasionally used. SKARBY and LINDBLOM examined the inner wall of the chest in extrapleural inflammations and demonstrated that a local swelling, corresponding to the abscess, existed. The examinations now described were performed mainly to look for possible changes in the soft tissue of the chest in pleuritis and empyema and to search for evidence for a differential diagnosis in inflammatory lesions. One would expect changes in the soft tissues to be more evident and pronounced in acute inflammatory processes and empyema than in ordinary pleuritis and in pure collections of fluid in the pleural cavity. In other lesions such as tumors, osteochondritis and fistulas the value of the examination has been estimated.

Technic

The technic is worked out as simply as possible. The patient may be examined in any posture — standing, sitting or supine. We have preferred

Submitted for publication Oct. 3, 1951.

to make the exposures in the sitting position in the chest-stand subsequent to the conventional examination of the lungs. The supine position has been used only for patients who are confined to bed. For comparison the two sides are examined on the same film divided into two (size 24 × 30 cm.). The patient should be placed in a semi-oblique position with the back against the casette and rotated 45° forward. The two sides must be turned at the same angle, otherwise the structure will be unequally projected and the one may seem broader and thicker than the other. It may be necessary to make two exposures in different degrees of obliquity in order to visualize the soft tissue at the most suitable angle. In general, the soft tissue corresponding to the dorsal axillary line should be examined. In women care must be taken to turn the breast away to avoid overlapping of the shadows. The arm must be kept aside and, in the prone position, rotated inwards. They should remain at the same level on each side and not be placed above the head as the scapulae then move laterally and may cover the axillary soft tissue. We have used 60 kv. 200 ma, distance $1^1/_2$ m. Exposures with a moving grid seem to give about the same results as those made without any secondary screening. A convenient exposure is soon obtained, and we have found a reliable criterion for an adequate quality of the films to be a clear outlining of the structures by the skin. Attention should be given to the processing so that the films are not overdeveloped.

Anatomical Considerations

A dense narrow band, the serratus muscle, stretches close to the thoracic wall from the axilla down towards the flank. The lateral contour of this muscle often has a wave-like appearance. Parallel to this and more laterally, a long, band-like, more regular density is observed corresponding to the latissimus dorsi. Between these two muscles a clear zone, due to a fat layer, is formed. More laterally the subcutaneous fat and the skinline bound the field. (Fig. 1.) All these structures are nourished by branches of the intercostal arteries, which may be definitely shown in cadaver specimens after the injection of a contrast medium into the aorta. On the original films the smallest vessels are observed running outwards to the subcutaneous fat and the skin.

Material

A great number of patients with fluid in the pleural cavity and inflammatory processes in the lung parenchyma have been examined by this method. The material comprises 35 cases of pleurisy, mainly of tuberculous origin. Clinical experience teaches that in some cases of pleurisy

Fig. 1. Soft tissue film of the chest. Contrast injected in the aorta. Inter-costal arteries penetrating the chest wall and running out to the skin. (Specimen).

Fig. 2. Soft tissues of the chest in a case of empyema, showing edema. Space between muscles obliterated. Network-like designs in subcutaneous tissue. Similar findings have not been observed in pleurisy.

percussion may give a more decreased resonance than would be expected from the amount of fluid present. Changes in the soft tissue could thus be anticipated, but positive findings have so far been scanty. In some

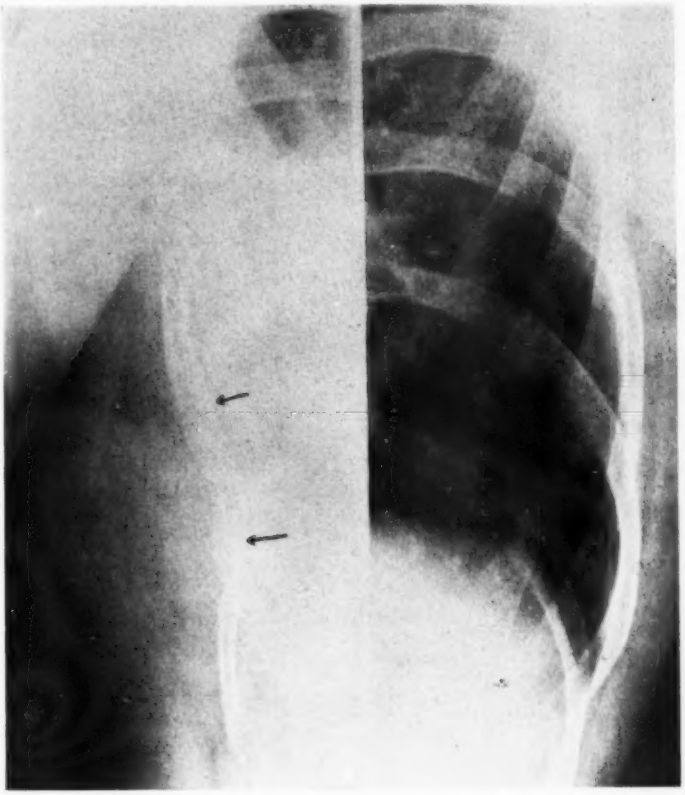

Fig. 3 a. Fig. 3 b.

Fig. 3 a. Changes in the soft tissues in a case of a costal metastasis. Edema and hyperemia caused by the tumor infiltration.
b. Left side for comparison.

instances a slight edema has been observed and in one case, a thickening of the »skin-line» could be demonstrated.

In empyemas the positive findings have also generally been few. However, in some instances marked changes were found in the soft tissues right out as far as the skin. (Fig. 2.) The findings are very similar to those in acute inflammatory processes followed by edema. The clear zone between the serratus and the latissimus muscles is obliterated and reticulated structures may be observed in the subcutaneous fat layer.

The most pronounced changes were visible in a case of costal destruction. A conventional film showed a medium-sized collection of fluid in

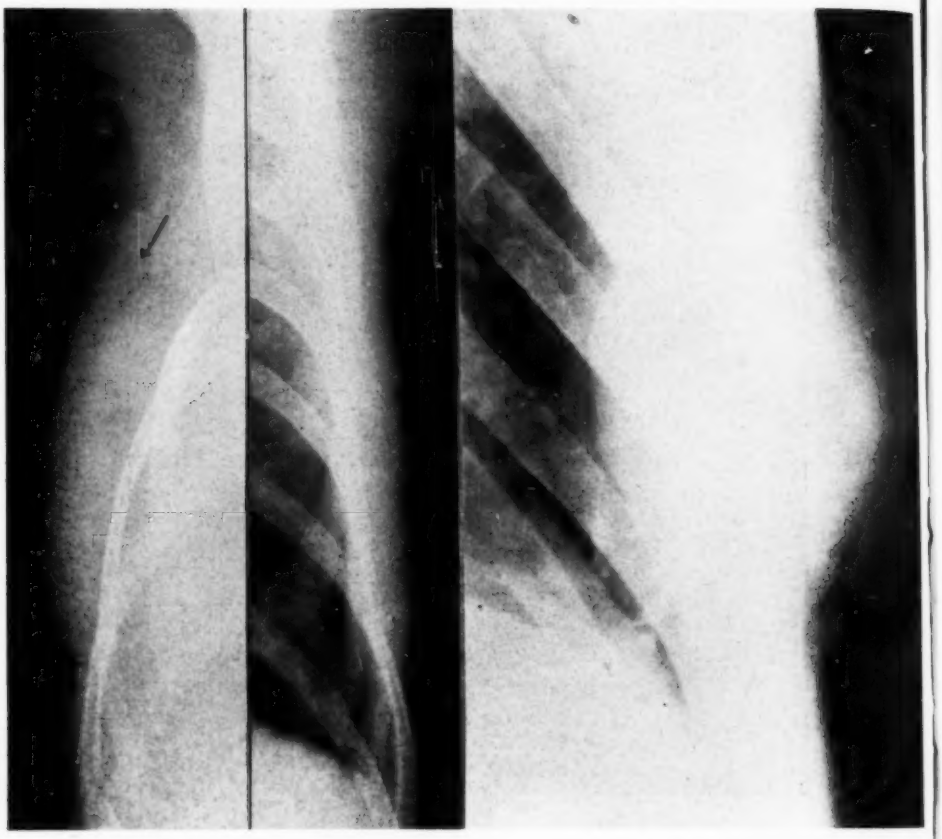

Fig. 4 a. Fig. 4 b. Fig. 5.

Fig. 4. a. Abscess in the subcutaneous tissues after thoracoplasty.
b. Sound side for comparison.

Fig. 5. Thoracic tumor showing extrapleural and subcostal swelling.

the pleural cavity and the diagnosis was pleurisy. However, re-examination revealed a thickening and broadening of the soft tissues and blurring of the muscular borders. On one of the films, a little more exposed, a local defect was observed in the 5th rib corresponding to the axillary line. (Fig. 3.) Biopsy revealed a metastasis probably from a hypernephroma. Thus the diagnosis of tumor infiltration was made indirectly from the soft tissue examination.

In a case in which thoracoplasty had been performed, a localized

Fig. 6. Thickening of the soft tissue in a case of coarctation. Tortuous vessels present on the original film.

thickening of the soft tissues with a corresponding complete blurring of the intermuscular spaces was observed. This opacity proved to be an abscess which subsided after surgical treatment. (Fig. 4.)

As pointed out by SKARBY and LINDBLOM, extrapleural thickening and subcostal swellings in cases of thoracic tumors and abscesses may be very well shown on soft tissue films. (Fig. 5.)

The possibility of showing the tortuous vessels in the soft tissue of the chest in cases of *coarctatio aortae* is also of interest. PEREIRAS and CASTELLANOS have demonstrated such changes by means of a contrast medium injected retrogradely into the aorta. Only one case of coarctation was available for soft tissue investigation in this material and the films did not show the changes satisfactorily enough for detailed reproduction. (Fig. 6.) Further experience in this field may provide a new diagnostic aid in this lesion.

Notching of the ribs is certainly pathognomonic evidence of this lesion, but changes in the ribs are lacking in at least 20 % of the cases; in such instances soft tissue films may give decisive support for the diagnosis.

SUMMARY

Examinations of the soft tissues of the chest are described. Films are made with the patient supine on a Bucky table or sitting in an ordinary chest-stand. The method may be valuable in differentiating various lesions of the chest, such as abscesses, tumors and empyemas. Soft tissue changes in a case of coarctation are described.

ZUSAMMENFASSUNG

Untersuchungen der Weichteile der Thorax sind beschrieben. Die Aufnahmen wurden in liegender Stellung am Trochoskop, oder in sitzender Stellung gemacht. Die Metode kann für die Entdeckung von Tumoren, Abscessen und Empyemen wertvoll sein. Weichteilbefunde in einem Fall von Coarctatio sind beschrieben.

RÉSUMÉ

Description des parties molles du thorax. Les clichés sont pris avec le malade couché sur une »table de Bucky» ou assis dans une position thoracique ordinaire. Le procédé peut avoir de l'importance pour distingner les diverses affections du thorax, telles que abcès, tumeurs et empyèmes. Les altérations survenues dans les parties molles au cours d'un cas de coarctation aortique sont décrites.

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FROM THE RADIOLOGICAL CLINIC (DIRECTOR: PROFESSOR CARL KREBS) OF THE UNIVERSITY OF AARHUS, DENMARK

ANOMALIES OF THE RIGHT DOME OF THE DIAPHRAGM

Report of Two Unusual Cases

by

C. E. Gudbjerg

During recent years diaphragmatic anomalies seem to have occurred with increasing frequency. However, this increase is only apparent and must be taken as an expression of improved diagnostic technique, notably in the field of radiology.

The anomaly is most frequently localized to the left dome of the diaphragm and the literature contains few reports of malformations of the right dome. This is due partly to the fact that the right pleuroperitoneal aperture is closed at an earlier stage of fetal life than the left and partly to the buffer action of the liver, which protects against traumas. The following cases are on record in more recent Scandinavian literature. NEIJ (1941) reported a case of right-sided incarcerated diaphragmatic hernia in which the diagnosis was verified at autopsy, WULFF (1945) a case which was cured by operation, THORELL (1945) a hernia in the Morgagnian foramen and finally, POPPE (1946) published two cases of right-sided diaphragmatic hernia of unquestionable congenital origin. In none of these cases was there herniation of the liver, although such a case was described by WAGNER (1946).

A clear classification of the anomalies of the diaphragm does not exist, presumably because some uncertainty prevails with regard to the pathogenesis. Thus, most authors divide the hernias into congenital, acquired and traumatic types; this classification seems less appropriate, since the acquired type of hernia is presumably always of congenital origin. The classification of all diaphragmatic anomalies may be simplified as follows:

Submitted for publication, Sept. 13, 1951.

- Diaphragmatic anomalies
  - Diaphragmatic hernia
    - Congenital
      - True (with hernial sac)
      - False (without hernial sac)
    - Traumatic (stab wounds, gunshot wounds, traffic accidents, etc.)
  - Relaxation of the diaphragm
    - Congenital (defective development of the musculature)
    - Paralytic (resection of the phrenic nerve, tumors, etc.)
  - Absence of the diaphragm

Own Cases

The first of the following two cases is an example of true congenital right-sided diaphragmatic hernia and the second, of congenital relaxation of the diaphragm with eventration of the right lobe of the liver.

Case 1. Female (2918/51), aged 53 years. For many years, particularly in the spring and autumn, had had a slight cough and functional dyspnea; during the previous year had had a feeling of retrosternal oppression on exertion; no other symptoms, notably no fatigue, loss in weight or dyspneic discomfort; no history of trauma. At a routine tuberculosis examination a »shadow» was found in the right lung, for which reason the patient was admitted to the Surgical University Clinic, Aarhus. Roentgen examination of the lungs disclosed a mandarin-sized, well-defined, regular, rounded density to the right of the heart just above the diaphragm (fig. 1). In the lateral view it was seen to be situated anteriorly in close contact with the thoracic wall (fig. 2).

Thoracotomy was performed (I am indebted to Professor N. Blixenkrone-Moller for permission to report this and the following case and make use of the descriptions of the operations): It was seen that the density was a hernia, 6.5 cm in diameter, which had forced its way through the Morgagnian foramen. It consisted of preperitoneal fat surrounding a small, empty hernial sac. It was excised, and the diaphragmatic defect, which admitted two fingers, was closed with silk sutures. The patient was discharged fully recovered.

Case 2. Male (3305/51), aged 61 years. Had always been well until 3 years previously when oppressive pain below the right costal margin radiating to the back suddenly developed; this subsided spontaneously in the course of three weeks. No history of trauma. One month before admission he again developed severe pain, this time in the upper part of the epigastrium, no relation to food; no nausea or eructations; appetite good and no loss of weight. During the preceding month he had had moderate functional dyspnea but no cough or precordial pain. He had been examined at the local hospital for his »stomach trouble»; the fluoroscopic examination revealed a tumor of the right lung and he was admitted to Aarhus Municipal Hospital. Chest roentgenograms showed a massive, homogeneous density, almost the size of a clenched fist, lying laterally at the right base. Above and medially it was well-defined and rounded; below it was confluent with the shadow of the diaphragm (fig. 3). In the lateral view it was seen to be situated

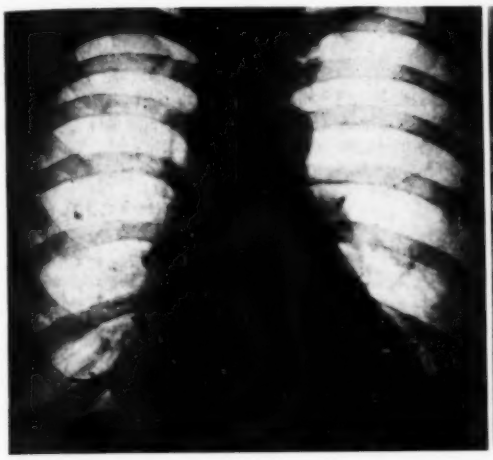

Fig. 1. Right-sided diaphragmatic hernia through the Morgagnian foramen, consisting of preperitoneal fat containing a small hernial sac.

Fig. 2. Same case as figure 1, seen from the right side.

Fig. 3. Right-sided relaxation of the diaphragm with eventration of the right lobe of the liver.

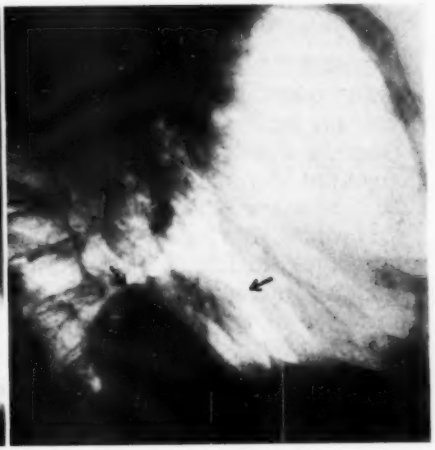

Fig. 4. Same case as figure 3, seen from the right side.

posteriorly in the lung, although not extending to the thoracic wall (fig. 4). The patient was transferred to the Surgical University Clinic for operation. Thoracotomy (BLIXEN-KRONE-MØLLER): It appeared that the lesion was a local relaxation, the size of half a palm, of the central portion of the diaphragm. The affected area was only 1 mm thick and through it there was a large abdominal protrusion. The diaphragm was opened and it then appeared that the prominence was a portion of the right lobe of the liver, which had changed form in the course of time. The opening was closed and a regular contour obtained by doubling the musculature of the diaphragm in this region; the patient made an uneventful recovery and was discharged.

As described, the *symptoms* were moderate in both cases and had not caused much discomfort. In both cases the affection was disclosed at a casual examination. On the whole, the symptomatology of diaphragmatic anomalies, notably those of the right side, is uncharacteristic. In traumatic cases, the immediate symptoms are often referable to the trauma itself, *e. g.* shock or pain; when these symptoms subside, the affection may persist asymptomatic for a long time or the symptoms may be slight dyspeptic reactions, such as a feeling of oppression after meals or occasional vomiting; cardiopulmonary discomforts, notably functional dyspnea, cyanosis, and retrosternal oppression may be experienced. An essential feature in the symptomatic picture is most frequently a combination of abdominal and thoracic symptoms; this should always suggest the possibility of a diaphragmatic anomaly.

Citing GREENWALD & STEINER, THORELL states that the distribution of diaphragmatic hernias is as follows:

Trigonum lumbocostale of Bochdalek	52.7	per	cent
Hiatus oesophageus	20.0	»	»
Centrum tendineum	12.8	»	»
Complete defect of left diaphragmatic dome	10.9	»	»
Trigonum sternocostale of Morgagni	3.6	»	»

HARRINGTON (cited in SHANKS & KERLEY) in 404 operated cases of diaphragmatic hernia reported only eight occurring through the Morgagnian foramen; of these, six were right-sided. These statements show the rarity of the case described.

I have been unable to find any exact statement of the frequency of congenital relaxation of the diaphragm in the literature. FELDMAN characterized the affection as extremely rare, while SHANKS & KERLEY wrote that congenital relaxation of the diaphragm »occurs on the left side almost exclusively». VERBRYCKE reported seven cases, all on the left side, and cited EPPINGER, who stated that the ratio of occurrence between diaphragmatic hernia and congenital relaxation of the diaphragm is 37:1.

The only case on record which resembles the case of congenital relaxation presented here is the one reported by WAGNER. However, in his

case the affection was not a congenital defect of the musculature of the diaphragm but a true hernia.

My inability to find a case of the congenital right-sided relaxation of the diaphragm reported in the literature confirms the rarity of the condition.

SUMMARY

The author presents a classification of diaphragmatic anomalies and reports two cases — one of true congenital right-sided hernia through the Morgagnian foramen and one of congenital right-sided relaxation of the diaphragm with eventration of the right lobe of the liver. Both cases gave only moderate symptoms and were both disclosed on casual examination.

ZUSAMMENFASSUNG

Der Verf. gibt eine Klassifikation der Zwerchfellanomalien an und schildert zwei Fälle — einen mit einer echten kongenitalen rechtsseitigen Hernie durch das Foramen Morgagni und einen weiteren mit kongenitaler rechtsseitiger Relaxation des Zwerchfelles mit Eventration des rechten Leberlappens. Beide Fälle gaben nur geringe Beschwerden und beide wurden als Nebenbefunde bei der üblichen Untersuchung entdeckt.

RÉSUMÉ

L'auteur présente une classification des anomalies diaphragmatiques et rapporte deux cas — l'un de véritable hernie congénitale à droite par le trou de Morgagni et l'autre de distension congénitale de la coupole diaphragmatique droite avec éventration du lobe hépatique droit. Les deux cas ne donnaient que peu de symptômes et ne furent décelés que par hasard.

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FROM THE RESEARCH LABORATORIES OF THE RADIUM CENTRE FOR JUTLAND AND THE ROENTGEN DEPARTMENT OF THE MUNICIPAL HOSPITAL (DIRECTOR: PROFESSOR CARL KREBS), AARHUS, DENMARK

CARCINOGENIC EFFECT OF SULFONAMIDES[1]

by

P. Bjerre Hansen and *J. Bichel*

A carcinogenic effect of sulfonamides has sometimes been suggested because of the similarity of the structural formulae of these compounds and the carcinogenic substances of the aniline-dye group. Experimental investigations concerning the possible carcinogenicity of the sulfa drugs are strikingly few. Furthermore, a certain disagreement exists between the results of the few observations published so far. If the sulfa drugs really possess carcinogenic potency, be it even slight, it would appear important to make an attempt to determine the tumor-producing effect of different compounds in animals and thereby possibly obtain some idea as to the risk of using the sulfonamides in the treatment of infection in human subjects.

Previous Experiments

LEWIS (1938) injected sulfanilamide suspended in olive oil into the right axilla of two-to-three-month-old mice of C_{57} and C_3H strains. Twenty-five animals received an injection of 12.5 to 25 mg and one month later a second injection of 12 mg. Ten mice were sacrificed 219 days after the first dose and showed no tumor development. The remaining mice were followed for 300 days, and as no tumors were observed, they were used for other experiments.

ZAMECNIK & KOLETSKY (1939) used mice of the Bar Harbour dba strain for similar experiments. A dose of 40—60 mg sulfanilamide was repeatedly injected into the left axilla of 52 mice every second or third

[1] Aided by grants from King Christian X's Foundation (to BJERRE HANSEN), the Lady Tata Memorial Trust, the Anders Hasselbalch Anti-Leukemia Foundation, and C. P. Schepler and Wife's Bequest, the Irma Foundation (to J. BICHEL).

Submitted for publication, Oct. 25, 1951.

week during a period of 4½ months. The total dose was 320 mg in each individual case. The sulfanilamide was given, finely ground, in a 20 % olive oil suspension. Twenty-three mice were sacrificed 12 months after the injections were started. No tumors were found. Nor did any of the 29 mice dying during the intervening months present any signs of neoplasms. — In another experiment injections of prontosil solubile were given to 19 mice. The total dose was 400 mg. None of the mice, of which eight survived more than 12 months, developed neoplasms.

FIGGE, WOLFE & FIGGE (1949) examined the influence of sulfanilamide, sulfathiazole, and sulfapyridine on cancer susceptibility in mice. More than 4,000 mice of different strains (A, C_3H, and C_{57}) were treated with various sulfonamides. The drugs were dissolved in the drinking water in a concentration of 3 g per litre. No significant effect on cancer susceptibility was observed. The experiments were extended over several generations of mice and disclosed a new phenomenon that the sulfa drugs inhibited reproduction. No explanation could be given. Sulfanilamide was the most active compound in this respect.

HAEREM (1940 and 1948) pointed out that the mice in LEWIS's and ZAMECNIK & KOLETSKY's experiments were pedigreed and had a natural genetic resistance to neoplasms. In his own experiments HAEREM used Swiss albino mice from Bar Harbour. These animals are not pedigreed, but the spontaneous incidence of cancer is low. To ensure slow absorption, lard was used as the suspending agent. Twenty mice received 15 mg sulfanilamide »on two occasions». Spindle-cell sarcoma developed at the site of injection in two mice dying 222 and 261 days, respectively, after the injections. In a later communication (1948), the results of repeated experiments were reported. Twenty mice of the same strain were injected with the same amount of sulfanilamide under identical conditions. This time, HAEREM found spindle-cell sarcomas in eight mice (40 %). These eight mice survived from 54 to 269 days. In the control group, injections with lard alone did not give rise to any tumor development. In the same report similar experiments on albino rats were mentioned. A group of 10 rats received an injection of 15 mg sulfanilamide into the left groin at the age of 14 weeks and another dose of 15 mg into the right groin at the age of 23 weeks. One animal developed a spindle-cell tumor in the left groin 9 months after the first injection, and a second rat developed a similar tumor in the right groin 11 months after the second injection. — A corresponding experiment was made with sulfapyridine. Forty rats were injected; three of them developed spindle-cell sarcomas at the injection sites and died 16, 19, and 20 months later, respectively. No tumors occurred in the control group.

Investigations concerning the carcinogenicity of sulfonamides were started at the Radium Centre in Aarhus in 1948. — Wistar rats, Aka

mice, and Rfl mice have been used as experimental animals. Wistar rats belong to a not strictly inbred strain and the tendency to spontaneous tumor development is low. The Aka mice are inbred and have a strong tendency to spontaneous neoplastic disease; leukemias and lymphosarcomas occur with a frequency of about 60—70 %. The Rfl mice are also an inbred strain, but with a very low frequency of spontaneous tumor growth. — The sulfa compounds investigated comprise sulfathiazole (4 experiments), a mixture of sulfamerazine (26 %), sulfadiazine (37 %) and sulfathiazole (37 %) (»Sulfacombin») (1 experiment), sulfamethylizole (1 experiment), and 6-sulfanilamido-4,6-dimethylpyrimidine (1 experiment). Male and female animals were equal in number in all the experiments. In the majority of the experiments injections of soluble compounds were employed. — The experiments are still in progress but a preliminary report on the results of the first six experiments is presented.

Experiment 1

One tablet of 6-sulfanilamido-4,6-dimethylpyrimidine, 50 cg, was implanted into the right axilla of 15 young Wistar rats. Tablets of the constituent parts alone were implanted into the right axilla of 15 control rats.

The first test animal died 9 months later with a huge abdominal lymphosarcoma with metastases in the liver. About 14 months after the implantation, another two animals died. One had a large adenocarcinoma in the right kidney, apparently without metastases; the other presented a spindle-cell sarcoma involving most of the spleen, but evidently originating from the retroperitoneal space. The remaining 12 rats died during the second year. No tumors were found. — The mortality in the control group was about the same as in the test group. The control animals did not develop any tumors.

Experiment 2

A single injection of »Injectabile Sulfathiazoli» was given into the right axilla of 10 Wistar rats (age approx. 6 months, weight approx. 200 g). The dissolving medium in Injectabile Sulfathiazoli is a NaOH solution with a pH = 9.8. The same amount (1 ml) of this solution was injected into the right axilla of 10 control animals. — The dose of sulfathiazole was 0.2 g = approx. 1 g per kg. This was evidently too large, as all the test animals died within 3—8 days of severe sulfathiazole intoxication. Autopsy revealed swollen hemorrhagic kidneys and deposits of sulfathiazole in the urinary system.

Experiment 3

The foregoing experiment was repeated with a smaller dose of sulfathiazole. Ten Wistar rats belonging to the same stock received a single injection of 0.1 g sulfathiazole (0.5 g per kg). Ten control animals were treated as described above. No symptoms of sulfathiazole intoxication were observed. The experiment was interrupted at the end of the 18th month.

Test Group:											
No.	21	22	23	24	25	26	27	28	29	30	
Life period	18	15	18	10	9	12	18	18	18	14	
Tumors	0	+	0	0	+	0	+	0	0	0	3+
Control Group:											
No.	31	32	33	34	35	36	37	38	39	40	
Life period	18	18	8	15	16	18	18	15	18	12	
Tumors	0	0	0	0	0	0	0	0	0	+	1+

Tumor development was found in two test animals dying 9 and 15 months, respectively, after the injection and in a third test animal, at autopsy, at the end of the experiment. These tumors were a renal carcinoma (No. 25), an abdominal lymphosarcoma (No. 22), and a spindle-cell sarcoma originating from the retroperitoneal space (No. 27). — One of the control animals (No. 40), which died 12 months after the injection, had a spindle-cell sarcoma in the pancreatic region, invading this gland and the liver. — The mortality in the two groups was about the same.

Experiment 4

A similar experiment was carried out with the mixed compound »Injectabile Sulfacombin». Twelve Wistar rats (age 4 months, weight approx. 125 g) received a single injection of 0.05 g sulfacombin = approx. 0.4 g per kg. Twelve control animals of the same stock were injected with a NaOH solution of the same pH. — The experiment was stopped 18 months later.

Test Group:													
No.	41	42	43	44	45	46	47	48	49	50	51	52	
Life period	11	18	10	18	18	18	10	18	11	18	18	13	
Tumors	+	0	0	0	0	+	+	0	0	0	0	0	3+
Control Group:													
No.	53	54	55	56	57	58	59	60	61	62	63	64	
Life Period	11	18	18	16	18	18	18	18	14	18	18	18	
Tumors	0	0	0	0	0	0	0	0	0	0	0	0	0+

Two test animals, Nos. 41 and 47, died before the 18th month from tumors. In No. 41 an adenocarcinoma of the left kidney was found, to-

gether with numerous metastases in the lungs. No. 47 also had a renal adenocarcinoma, a very large tumor nearly destroying the entire right kidney, with a few lung metastases. A third animal with a tumor was found among the animals sacrificed at the end of the experiment. In this case, No. 46, the tumor was a large mediastinal lymphosarcoma. — No tumor development occurred in the control group. — Again, the mortality was nearly equal in the two groups.

Experiment 5

In this experiment mice of the Aka strain were used. Eighteen mice (age approx. 2 months, weight approx. 20 g) were given a single injection of 0.01 g sulfathiazole into the right axilla (approx. 0.5 g per kg). Eighteen control animals of the same stock received injections of a NaOH solution of the same pH. The experiment was continued until all the animals had died.

Test Group:																			
No.	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	
Life period .	6	15	18	13	19	7	8	12	8	15	7	5	8	6	10	8	4	4	
Tumors	+	0	0	+	0	+	+	+	+	0	+	+	+	+	+	+	+	+	14+
Control Group:																			
No.	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	
Life period .	18	11	19	8	16	8	9	11	7	12	15	17	11	10	12	12	14	18	
Tumors	0	+	0	+	0	+	+	+	+	0	+	0	+	+	+	0	+	0	11+

The so-called tumors were in all cases in both groups leukemic lesions in the mesenterial, mediastinal, and peripheral lymph nodes, and to a varying degree, in the spleen, thymus, and liver. In some cases the lesion seemed to be more localized, confined to a single group of lymph nodes and then resembling a lymphosarcoma. Both lymphatic and stem-cell leukemias were represented, the lymphatic type being the more common. In several cases an enlargement of the thymus was the most prominent feature. — The difference between the numbers of »tumors» in the test and the control groups is not significant, since the tumor frequency was within the normal range of spontaneous leukemia in Aka mice (about 60—70 %). — But an acceleration of the development of malignant disease apparently took place in the test group. The average life period after the injection was, in the 14 test animals dying with »tumors», 7.6 months, as compared with an average of 10.4 months for the corresponding control animals. The figures for the animals which died without »tumors» were 16.5 and 16.2 months in the test and the control groups, respectively.

Experiment 6

Peroral administration was tried in this experiment. Twelve Aka mice received a daily dose of 0.2 ml of a 1.65 % solution of sulfathiazole introduced into the stomach by means of a small tube. This was continued for 2 weeks. The daily dose was 0.0033 g and the total dose 0.046 g sulfathiazole (0.165 g and 2.31 g per kg). Twelve control animals were treated in the same way with the corresponding NaOH solution. — The experiment was interrupted 16 months later.

Test Group:													
No.	102	103	104	105	106	107	108	109	110	111	112	113	
Life period	7	8	8	16	9	5	7	15	4	15	10	11	
Tumors	+	+	+	0	+	+	+	0	+	0	+	+	9+
Control Group:													
No.	114	115	116	117	118	119	120	121	122	123	124	125	
Life period	9	5	9	15	8	16	10	16	16	13	13	16	
Tumors	+	+	+	+	+	0	+	0	0	0	+	0	7+

As in experiment 5, the »tumors» were of a leukemic nature in all cases. Just as in experiment 5, no significant difference was present between the numbers of »tumors» in the two groups, but a conspicuous acceleration of the tumor development was seen. The average life periods of the animals which died before the end of the experiment were 7.6 months and 9.7 months in the test and the control groups, respectively.

Experiment 7

Mice of the Rfl strain were used for a new series of sulfonamide injections. Twelve injections of sulfamethylizole were given into the right axilla of 20 mice, three times weekly during four weeks. The dose was 0.013 g per injection (approx. 0.5 g per kg, the average weight of the mice being about 25 g). — As in the preceding experiments the dissolving medium of the Lucosil preparation was administered to the control group. — The experiment was stopped 12 months after the last injection.

Test Group:																				
No.	126	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
Life period	13	1	1	13	13	10	13	13	11	13	10	10	13	13	13	5	11	13	13	11
Tumors	0	0	0	0	+	+	0	0	0	0	0	0	+	0	0	0	+	0	0	0	4+
Control Group:																				
No.	146	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65
Life period	13	13	13	13	13	6	13	13	13	13	13	13	11	13	10	13	13	10	10	13
Tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0+

Two of the test animals (Nos. 142 and 131) died of tumors 5 and 10 months after the last injection. At autopsy at the end of the experiment, another two animals with tumor development were found (Nos. 130 and 138). In three cases, the tumors consisted of round-cell sarcomas in the mesenterium and the retroperitoneal space (Nos. 131, 138, and 142). In the fourth case (No. 130) a plasmacytoma was found in an enlarged cervical lymph node. In addition, an adenoma of the right lung was found in No. 131. — No tumor development could be demonstrated in the control animals. — Two of the control animals died only one month after the last injection. The cause of death was pneumonia. In all the other animals from both groups no pathological changes of any interest were observed.

Discussion

In the experiments in which animals without tendency to spontaneous tumor development were used, a moderate but, in our opinion, manifest carcinogenic potency of the sulfonamides was demonstrated.

The tumors which developed in the test animals in the first three experiments with Wistar rats (experiments 1, 3 and 4) were, in four cases renal adenocarcinomas, in three cases lymphosarcomas, and in two cases spindle-cell sarcomas. In the corresponding control groups only one tumor, a spindle-cell sarcoma, was found. This gives an incidence of approx. 25 % in the test group as compared with approx. 3 % in the control group. The relatively large number of cancers of the kidneys is remarkable and recalls the carcinomas of the bladder in aniline workers. The bladders of all the experimental animals were examined, but no signs of tumors were found. The experiment with Rfl mice (experiment 7) showed tumor development in 20 % of the test animals. These tumors were, in three cases round-cell sarcomas, and in one case a plasmacytoma.

In the experiments with the Aka mice, animals with a very high spontaneous incidence of malignant disease, an acceleration of tumor development by two or three months was seen (experiments 5 and 6). This seems also to suggest a certain carcinogenic effect of the sulfonamides.

The various sulfonamide compounds used showed no difference in the tumor-producing effect. Possibly, this might hardly be expected from six experiments only. The mode of administration did not seem to influence the results. It is remarkable that tumors never occurred at the site of the injections or at the site of the implantation of tablets in the first experiment. The latter possibility especially was expected in view of the results of HAEREM's experiments. Careful examination of the region in question was, however, absolutely negative. However, in the main

our experiments seem to confirm the results obtained by HAEREM, but experiments on a much larger scale will be needed to evaluate the carcinogenicity of different sulfonamides.

Finally we want to stress that our experiments are animal experiments and do not permit conclusions as to any definite carcinogenic effect of sulfonamides in man.

SUMMARY

The carcinogenic potency of sulfonamides has been investigated experimentally. In mice and rats without tendency to spontaneous tumor development, the occurrence of tumors in about 20—25 % of the test animals is demonstrated in contrast to a few per cent in the control animals. In mice with a pronounced tendency to spontaneous tumor development, an acceleration of this process is seen in the test animals treated with sulfonamides. The carcinogenic effect seems to be independent of the mode of administration, and the various sulfa-compounds examined give the same results.

ZUSAMMENFASSUNG

Die karzinogene Potenz der Sulfonamide wurde experimentell untersucht. Bei Mäusen und Ratten ohne Tendenz zu spontaner Tumorbildung konnten Tumoren in etwa 20—25 % der Versuchstiere nachgewiesen werden; im Gegensatz hierzu fand man bei Kontrolltieren Tumor nur in wenigen Prozent. Bei Mäusen mit ausgesprochener Tendenz zur Bildung von Spontantumoren wurde eine Beschleunigung dieses Prozesses bei den mit Sulfonamid behandelten Tieren beobachtet. Der karzinogene Effekt scheint unabhängig von der Administrationsweise zu sein und die verschiedenen untersuchten Sulfaverbindungen geben die gleichen Resultate.

RÉSUMÉ

Le pouvoir cancérigène des sulfamides a été examiné expérimentalement. Chez des souris et des rats sans tendance au développement de tumeurs, l'on décèle la présence de tumeurs chez 20 à 25 % des animaux en expérience, tandis que chez les animaux témoins le taux se limite à quelques pour-cent. Chez les souris prédisposées au développement de tumeurs spontanées l'on constate une accélération du processus chez les animaux à qui on administre des sulfamides. Le pouvoir cancérigène des sulfamides semble être indépendant du mode d'application. Les divers composés examinés ont donné le même résultat.

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DU RÔLE DU SEXE ET DE L'ÂGE DES SOURIS DANS LA TRANSMISSION DU SARCOME KREBS, RASK-NIELSEN & WAGNER

Recherches supplémentaires

par

Johannes Harbo

Lorsque nous avons tiré les conclusions des recherches publiées en 1942 sur la leucose des souris de KREBS, RASK-NIELSEN & WAGNER (appelée par les auteurs: lymphomatosis infiltrans leucaemica et aleucaemica), nous avions dû, dans la discussion des résultats des expériences sur la résistance des souris à la prise et à l'évolution de l'affection transmise par injection intrapéritonéale de liquide d'ascite provenant d'animaux porteurs de tumeurs abdominales, et contenant des cellules, réserver l'influence possible sur la réceptivité des animaux servant aux expériences, de leur sexe, et avant tout, de leur âge. Les résultats des recherches sur ces deux questions, qui sont consignés dans les deux tableaux ci-joints, seront mentionnés brièvement ci-dessous. Toutes les souris femelles employées dans nos recherches actuelles et précédentes étaient des animaux vierges.

Tableau 1

Souris mâles			Souris femelles			Divergence % ($\alpha \div \beta$)	L'erreur statistique (moyenne) de la divergence % (σ)	($\alpha \div \beta$) divisé par (σ)
Greffes		% de succès (α)	Greffes		% de succès (β)			
réussies	faites		réussies	faites				
49	60	81.7	42	57	73.7	8.0	7.7	1.0(4)
50	63	79.4	68	83	82.0	÷ 2.6	6.6	÷ 0.3(9)
70	94	74.5	61	90	67.7	6.8	6.7	1.0(1)
15	23	65.2	39	50	78.0	÷ 12.8	11.0	÷ 1.1(6)

Soumis à la Réd. le 29 août 1951.

Tableau 1, qui contient les résultats de 4 expériences, où ont été comparés des groupes de souris, identiques en ce qui concerne l'âge et l'origine, mais différentes quant au sexe, montre clairement sans autre analyse statistique, qu'on ne peut constater aucune divergence systématique entre les pourcentages de succès; autrement dit que *le sexe de l'animal, aux âges qui sont représentés à nos expériences de résistance, n'a aucune influence sur la résistance naturelle contre la prise de la tumeur.*

Quant à l'influence de l'âge, c'est spécialement l'importance d'une différence de 2 mois, qui nous intéresse dans ce travail. Les résultats de toutes les expériences que nous avons faites, se dégagent du *tableau 2*. Nous avons comparé des groupes de souris qui sont identiques quant à l'origine et au sexe, mais différentes quant à l'âge. Dans les 8 expériences que nous avons faites, il y avait des différences d'âge d'environ 50 jours jusqu'à environ 95 jours.

Tableau 2

Différence d'âge entre les groupes, jours.	Souris jeunes			Souris plus âgées			Divergence % ($a \div \beta$)	L'erreur statistique (moyenne) de la divergence % (σ)	($a \div \beta$) divisé par (σ)
	Greffes		% de succès (a)	Greffes		% de succès (β)			
	réussies	faites (a)		réussies	faites (b)				
61	70	79	88.7	45	60	75.0	13.7	6.5	2.11
63	98	112	87.5	84	109	77.0	10.5	5.1	2.02
96	61	83	73.5	44	75	58.7	14.8	7.5	1.97
79	51	75	68.0	54	77	70.1	÷ 2.1	7.5	÷ 0.28
71	89	104	85.6	65	80	81.3	4.3	5.5	0.78
75	34	47	72.3	37	43	86.1	÷ 13.8	8.6	÷ 1.60
64	27	32	84.4	14	15	93.4	÷ 9.0	10.4	÷ 0.86
50	21	29	72.4	11	19	57.9	14.5	13.9	1.04

On peut faire une évaluation des matériaux sur la base des chiffres de la dernière colonne du tableau ($[a : \beta] : \sigma$), en formant pour les expériences, qui doivent entrer dans l'évaluation, l'expression

$$x = \frac{\sum \frac{a : \beta}{\sigma}}{\sqrt{n}},$$

dans laquelle n signifie le nombre des expériences comprises dans l'évaluation. Si en effet la probabilité d'une réussite dans chaque expérience était la même pour les deux âges comparés, les différentes valeurs de

l'expression $(\alpha \div \beta) : \sigma$ pourraient être considérées comme des quantités accidentellement variables avec la valeur prévue 0 (zéro) et l'erreur moyenne 1 (un). Leur somme $\Sigma (\alpha : \beta) : \sigma$ devrait en ce cas avoir la valeur prévue 0 et l'erreur moyenne $\sqrt{n}$. Si on trouve la proportion x d'une valeur absolue d'environ 3 ou plus, on aura le droit de regarder les différences entre les pourcentages de succès dans les expériences en question comme significatives au point de vue statistique — et autrement pas.

Le calcul des différentes valeurs de l'expression x donne les résultats suivants:

Pour toutes les 8 expériences comprenant des différences d'âge d'environ
50 jours jusqu'à 95 jours ..... $x = 1.83$;
pour 6 exp. comp. des diff. d'âge d'environ 50—75 jours ..... $x = 1.42$;
» 5 » » » » » » 60—75 jours ..... $x = 1.10$.

Ces chiffres montrent que bien qu'on ne puisse pas laisser de côté la possibilité que la sensibilité à l'affection en question diminue lentement selon l'âge des souris greffées, *cette différence de sensibilité supposée entre les différentes classes d'âge n'est pourtant pas, à une différence d'âge d'environ 2 mois, d'une telle grandeur, qu'elle puisse être constatée avec certitude.* Comparant cela aux différences de résistance assez remarquables, que nous avons autrefois trouvées, dans nos expériences précédentes avec des extraits de tumeur dépourvus de cellules, entre les animaux traités avec des extraits et les témoins non-traités, on peut constater que le résultat de ces recherches est venu appuyer et confirmer essentiellement les résultats de nos expériences et nos conclusions précédents.

Dans le calcul du résultat des recherches sur l'influence du sexe entrent 520 souris. Le résultat des recherches sur l'influence de l'âge a été dérivé sur une base de recherches avec 1,328 souris.

RÉSUMÉ

Les recherches actuelles sur l'influence du sexe et de l'âge sur la sensibilité des souris d'expérience à la transplantation de la lymphomatosis infiltrans leucaemica et aleucaemica (ainsi nommée par KREBS, RASK-NIELSEN & WAGNER) sont venues appuyer et confirmer essentiellement les conclusions faites sur la base des résultats des expériences publiées en 1942 par KREBS, THORDARSON & HARBO.

SUMMARY

The present investigation deals with the possible influence of sex and age of experimental animals (mice) on the transmissibility of lymphomatosis infiltrans leucaemica & aleucaemica (KREBS, RASK-NIELSEN & WAGNER). The findings reported support and confirm essentially the conclusions drawn from the experimental results published in 1942 by KREBS, THORDARSON & HARBO.

ZUSAMMENFASSUNG

Die Ergebnisse der vorliegenden Untersuchungen über die möglichen Einflüsse des Geschlechtes und des Alters auf die Empfänglichkeit von Versuchstieren gegenüber Transplantatationen von Lymphomatosis infiltrans (KREBS, RASK-NIELSEN und WAGNER) haben die Schlussfolgerungen aus den von KREBS, THORDARSON und HARBO früher veröffentlichten Versuchsresultaten wesentlich unterbaut und bestätigt.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: I. SALLINEN) OF THE MARIA HOSPITAL, HELSINKI, FINLAND

MULTIPLE JEJUNAL DIVERTICULA

by

Kalevi Kettunen

Diverticula of the jejunum are exceedingly rare. FRASER (4) put the frequency of diverticula in various parts of the gastrointestinal tract in the following order: (1) colon, (2) ileum (Meckel's diverticulum), (3) duodenum, (4) pharynx and esophagus, (5) stomach and (6) jejunum. Those occurring in the jejunum are most frequently situated near the ligament of Treitz and diminish distally in size and number. They are most often multiple and are found in numbers from a few to several hundreds in given cases. They are practically always of the hernia type: herniations of the mucous membrane through the muscular layer of the intestinal wall. The size of a diverticulum varies from a few millimeters to several centimeters in diameter. Diverticula of the jejunum are noted in all age groups, most cases being encountered in middle or late adult life.

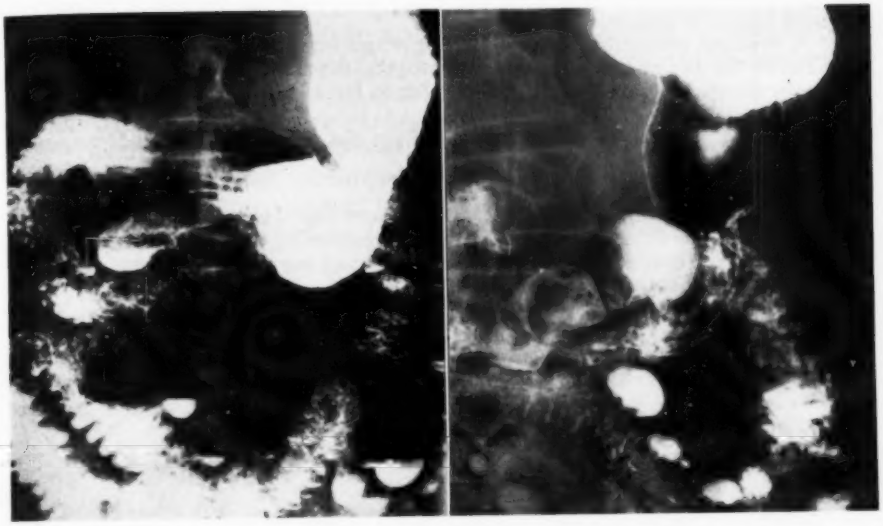
A study of the literature reveals the extreme infrequency of these lesions. EDWARDS (3), for example, found 9 cases of diverticula of the jejunum in 2,820 autopsies, and REINHARDT (8) only 3 instances of diverticulosis of the jejunum in 5,000 postmortem examinations. RANKIN and MARTIN (7) stated that jejunal diverticulosis was found only once in approximately 25,000 roentgen examinations. WILKERSON (12) was able to find 322 cases of jejunal diverticula in the literature up to 1948.

Report of Cases

Case I: E. E.; male, aged 63. Four months constant history of diarrhea with 3 loose stools a day and of rumbling noises in the abdomen after food; no other digestive symptoms; no pain, no nausea, and no vomiting; some loss of weight noticed; no relevant previous disease.

Physical examination: N. A. D.: the patient was well-developed and fairly well nourished. Laboratory findings were negative except for a complete absence of free hy-

Submitted for publication, Dec. 15, 1951.



a. b.

Fig. 1. Case I. Roentgenograms showing multiple diverticula of jejunum: a) erect, b) supine position.

Fig. 2. Case II. Two diverticula in the duodenum and multiple jejunal diverticula (supine position).

drochloric acid in the stomach. No evidence of any lesion in the lower bowel detected by barium enema or proctoscopic examinations.

A roentgen examination of the esophagus and stomach gave normal findings; two diverticula the size of small apples were present in the third part of the duodenum and multiple diverticula varying in size from peas to large plums in the jejunum (Figs. 1 a—b).

The patient was treated with a low-roughage diet, and after a period of two weeks had relief of symptoms.

Case II: A. B.; female, aged 65. Fifteen years previously the patient was treated at another hospital for peptic ulceration. For the preceeding two years she had vomiting and pains in the upper abdomen. The symptoms were very severe at times, and were almost constant previous to examination.

Physical examination revealed only a small umbilical hernia and slight tenderness in the epigastrium. Roentgencgraphic examination of the upper gastrointestinal tract showed no changes in the esophagus or stomach. The opaque meal passed into the duodenum efter a delay of about ten minutes; two large diverticula were seen in the third part of the duodenum and multiple small diverticula in the jejunum (Fig. 2); four-hour examinations showed retention of barium in the diverticula.

Discussion

In the great majority of diverticulosis of the small intestine recorded in the literature the diagnosis had not been made before autopsy. In 85 of the 122 cases reported by Benson, Dixon and Waugh (1) the diverticula were found at autopsy, in 21, discovered at operation, in only 16 cases, revealed on roentgen examination. It is quite probable that many cases are overlooked on roentgen examinations; fluoroscopy of the stomach and duodenum should always include an investigation of the upper jejunal loops; if there be any clinical suggestion of disease of the small bowel, careful observation of its entire length is essential.

A relationship of jejunal and ileal diverticula to other congenital abnormalities elsewhere in the body has been described. Case (2) noted the frequent association of diverticulosis of the small bowel with diverticula elsewhere in the digestive tract. 11 of 25 cases reported by Ritvo and Votta (9) presented diverticula of the duodenum and small intestines. Of these, 8 were in the descending portion, 3 in the cap or bulb and 1 in the third part. One patient had two duodenal diverticula lying in the second and third parts, respectively. In both cases reported here there were two diverticula in the third portion of the duodenum.

Jejunal diverticula cause symptoms in a much smaller number of cases than duodenal diverticula, the reason being that the duodenum is fixed and the jejunum relatively free and motile, the constantly changing position of the ostia facilitating the emptying of the diverticula. Pain and flatulence have been cited by numerous authors as the usual symptoms of jejunal diverticula. The flatulence is the result of the retention of

intestinal contents in the diverticula. The pain may be due to the same cause or, if particularly severe and cramp-like in nature, to obstruction of the bowel by a large pouch. In case I, the absence of typical symptoms is noteworthy.

Diverticulitis of the jejunum has been reported by OVENS (6), RUDDER (10) and KOZINN and JENNINGS (5). Inflammatory disturbances may result in gangrene and perforation and adhesions to jejunal diverticula may cause acute obstruction. Other complications such as hemorrhage from the diverticula, rupture, foreign bodies and neoplastic diseases may be encountered.

When it has been decided that the diverticula cause symptoms the question of treatment may be divided into medical and surgical. If the patient is asymptomatic and there are no complications, surgical interference is not indicated. In case I, the dietary restrictions were sufficient to relieve the patient of symptoms.

SUMMARY

Two cases of multiple jejunal diverticula are reported. The signs were revealed on opaque meal examination, in the first case in a male with a history of diarrhea and in the second in a female complaining of epigastric pain and vomiting.

ZUSAMMENFASSUNG

2 Fälle mit multiplen Jejunaldivertikeln werden geschildert. Die Befunde werden durch Kontrastmitteluntersuchung erhoben, im ersten Falle bei einem Mann mit Durchfällen in der Anamnese und im zweiten Falle bei einer Frau mit Schmerzen in der Magengrube und Erbrechen.

RÉSUMÉ

Présentation de deux cas de diverticules multiples du jéjunum. Les signes radiologiques furent mis en évidence par un repas opaque. Le premier cas était celui d'un homme présentant une diarrhée de longue durée, le second celui d'une femme souffrant de douleurs épigastriques et de vomissements.

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FROM THE CLINICAL DEPARTMENT AND THE RESEARCH LABORATORIES, RADIUM CENTRE FOR JUTLAND (DIRECTOR: PROF. CARL KREBS), UNIVERSITY OF AARHUS, DENMARK

ACUTE HODGKIN'S DISEASE

by

Jørgen Kieler

The average duration of Hodgkin's disease subjected to roentgen treatment is reported to be 3—4½ years (1). The majority of cases are said to progress through three stages: (a) a period of latency, without symptoms, (b) a period of progression and generalisation during which symptoms of varying severity appear, and (c) a period of cachexia which precedes the death of the patient (2, 3). However, variations are wide and the average survival time affords little information about the individual prognosis.

The following classification, based upon the clinical course of the disease, has been formulated: (1) an acute form of a few weeks' to a few months' duration, (2) a rapid form of a few months' to two years' duration. (3) an average form of two to six years' duration and (4) a protracted form of more than six years' duration (4, 5).

Acute cases of Hodgkin's disease are rare. They are characterized by a fulminating, feverish course from the onset of the morbid manifestations. The stages rapidly merge, and the patients do not respond to therapy (5, 6, 7, 8, 9).

During the period from 1941 to 1951 a total of 239 cases of Hodgkin's disease have been treated at the Radium Centre, Aarhus. Of these, only 2 could be classified as acute.

Report of Cases

Case 1 (977/43): A male, aged 59: admitted to the Radium Centre on the 19th April, 1943.

September 1942: Lumbago. February 1943: herpes zoster of three weeks' duration, right lumbar region.

Aided by grants from the Lady Tata Memorial Trust, Anders Hasselbalch Anti-Leukaemia Foundation, and C. P. Schepler and Wife's Bequest, the Irma Foundation.

Submitted for publication, Oct. 30, 1951.

A month before the admission to the Radium Centre he had suddenly developed high fever (40° C) and later been admitted to hospital elsewhere; he had felt exhausted and had epigastric tenderness, nausea, anorexia, and had lost weight. On examination a mass below the right costal margin was felt and a preliminary diagnosis of cholecystitis made. As the sedimentation rate and the temperature remained elevated in spite of sulfonamide treatment, the patient was transferred to the Radium Centre for further examination.

Condition on admission: Two enlarged lymph nodes noted in the right axilla but no other sign of superficial lymph-gland enlargement. Upon abdominal palpation, a tumour the size of a walnut was felt above the umbilicus, and a somewhat larger mass just below the right costal margin; the spleen was enlarged (»two fingers»). Roentgen examination of lungs, intestines and gall bladder did not reveal anything abnormal. There appeared to be evidence of a diverticulum of the greater curvature of the stomach. R. B. C.: 3,270,000 (66 % hemoglobin); W. B. C.: 3,440 (neutrophils 88 %, lymphocytes 10 %, and monocytes 2 %). S. R.: 88 mm/one hour. The temperature fell during his stay in hospital from 39.2° to 37.6° (vespere).

Further examinations were considered, but on the 24th of April the patient suddenly developed severe epigastric pain, and became pale, restless, and perspired profusely. The pulse became imperceptible and in 3—4 minutes death ensued.

Autopsy findings: The cervical lymph-glands were slightly enlarged but not otherwise abnormal on section. The right axilla contained two firm lymph-glands and in the peri-esophageal connective tissue three firm nodes were found. The abdominal aorta was surrounded by numerous firm glands measuring up to 8 × 6 × 5 cm; the cut surface of a section was yellowish-white and covered with hemorrhagic spots. The lungs were edematous and there was evidence of old pleurisy on the right side; no fluid present. The pericardial sac contained 40 ml serous fluid. The myocardium was pale, dry and flabby. The coronary and pulmonary arteries were normal, without any signs of thrombosis or emboli. The endocardium was normal.

The spleen weighed 720 gm and measured 18.5 × 11.5 × 7 cm. It contained numerous solid white areas, measuring from 0.5 to 2 cm. The liver measured 34 × 22.5 × 8 cm. It was dark and dry on section but not infiltrated. The prostate gland was enlarged and hard; there was trabeculation of the mucosa of the bladder. The bone-marrow appeared red and hyperplastic; no evidence of bone destruction.

Microscopic examination: Lesions characteristic of Hodgkin's disease were found in the lymph-glands and the spleen. The lymph nodes showed complete loss of architecture, increase in reticular fibres and fibrosis. Lymphocytes, eosinophils, plasma-cells and Sternberg-Reed cells were numerous. There was evidence of Hodgkin's granulomatosis with hyaline degeneration in the spleen; numerous reticular cells and fibres together with infiltrations of lymphocytes, eosinophils and a few Sternberg-Reed cells, were noted.

Case 2 (3984/49): A male, aged 36; developed caries and recurring dental abscesses in the middle of the summer of 1948; in August 1949 all the teeth were extracted. In September there was tender and rapidly increasing enlargement of the cervical glands and he felt feverish. Three weeks later he noticed a tumour in the left axilla and complained of cough, expectoration and dyspnea; a week later swelling and redness of the left thoracic wall developed. The appetite decreased, and he lost weight; admitted to the Radium Centre on the 11th November, 1949.

Condition on admission: Large collections of enlarged cervical and occipital lymph-nodes present (see figure); lymph-gland enlargement also noted in both axillae and in the right femoral region. The skin of the neck and the thoracic wall, notably on the left

side, was edematous and red. There were signs of pleural and pericardial effusion, and a distinct pericardial »rub» was heard; spleen and liver not palpable.

Roentgen examination revealed considerable enlargement of the anterior mediastinum, slight displacement of the trachea to the right, and increased density of the perihilar and basal regions of both lungs.

R. B. C.: 3,130,000 (60 % hemoglobin). W. B. C.: 36,000 (neutrophils 82 %, eosinophils 3 %, lymphocytes 9 %, and monocytes 6 %). Thrombocyte count: 320,000. S. R.: 84 mm/one hour. Mantoux test: negative; antistreptolysine titer: normal (64).

The patient ran an intermittent type of fever that ranged between 36.8° and 38.9° C. Biopsy of a cervical gland was made; microscopic examination showed lesions typical of Hodgkin's disease. The patient received a total of 29 mg nitrogen mustard. The treatment was accompanied by nausea and vomiting.

Fig. 1.

He went rapidly downhill and had increasing dyspnea, not relieved by carbogen; died 19th November.

Autopsy findings: Numerous solid, white cervical glands measuring up to 3 by 4 cm and forming large conglomerates were noted. Similar nodes were present in both axillae, on the left side of the thorax, in the right femoral triangle, the pulmonary hili and the mediastinum as well as in the mesentery and the hepatic porta. The tonsils were hyperplastic, and glottic edema had caused marked narrowing of the upper respiratory tract. There was a high degree of pulmonary edema, and the lungs were invaded and in some parts compressed by the hilar glands.

A small hydropericardium and bilateral hydrothorax were found; the right pleural cavity contained one litre and the left, two litres of serous fluid. Except for a slight dilatation of the left ventricle the heart did not show any abnormality. The liver was enlarged (26 × 23 × 12 cm); otherwise normal. The spleen weighed 340 gm; on section it showed numerous white areas. The bone marrow appeared to be red; no bone destruction detected.

Microscopic examination: The lymph-glands showed numerous reticular fibres, fibroblasts, lymphocytes, eosinophils, and Sternberg-Reed cells. In the spleen there were small necrotic foci; Sternberg-Reed cells were abundant and plasma-cells and eosinophils present.

The liver showed signs of congestion; no abnormality of the kidneys noted.

[Comment

The classification of the various forms of Hodgkin's disease depends mainly on its duration. HOSTER and DRATMAN (10) stress the difficulties of giving accurate data concerning the duration of Hodgkin's disease since it is impossible to establish the time of onset even within a margin of months. They call attention to the fact that in chronic cases the

patients may live undiagnosed for years. In addition, the protean symptomatology of Hodgkin's disease makes it hazardous to fix the onset by possible coincidental symptoms.

It is well-known that after a long period of latency, during which glands, without causing symptoms, may become enlarged, cases may suddenly take a fulminating course terminating in death in a few weeks; such cases have undoubtedly been mistaken for acute forms of Hodgkin's disease (2, 11). However, this does not appear to justify the view, apparently held by ZIEGLER (2), that all so-called acute cases represent a fulminating terminating stage following a long asymptomatic period of latency; but it makes the classification of many cases uncertain.

The course of Case 1 resembled an acute infection with sudden onset and high fever. Cholecystitis was suspected. However, the rapid enlargement of the abdominal lymph-glands, of the liver and the spleen revealed the malignant nature of the disease although a final diagnosis was not made before autopsy. Death followed 5 weeks after the apparent onset of the disease. The immediate cause of death was somewhat obscure. Clinically, acute peritonitis with cardiac failure was suspected, although the autopsy findings offered no obvious explanation. The pathological findings were: Hodgkin's disease with involvement of the spleen as well as the retroperitoneal, mediastinal, and axillary lymph nodes; edema of the lungs and hydropericardium; parenchymatous degeneration of the liver and the myocardium; old pleural fibrosis, hypertrophied prostate, and trabeculated mucosa of the urinary bladder.

The dominating feature of Case 2 was the rapidly progressing growth of lymph-glands followed by edema of the neck and the thoracic wall, hydrothorax and pericarditis, and terminal edema of the lungs and the glottis. Cervical lymph-gland enlargement was first observed; 3 weeks later the patient began to cough and expectorate, and at the same time enlargement of the axillary and femoral glands was noted. Eight to nine weeks after the onset of the cervical lymph-gland enlargement, the patient died from suffocation caused by edema of the glottis and the lungs. The pathological findings were: Hodgkin's disease with involvement of the spleen and the cervical, mediastinal, axillary, abdominal, and femoral lymph nodes; glottic and pulmonary edema, hydrothorax and hydropericardium; congestion and hyperplasia of the liver, and myocardial hypertrophy.

In both the cases reported the past histories revealed symptoms which may have been related to the actual disease. Thus, in the first case, its onset was preceded 6 months by lumbago; in view of the mainly retroperitoneal situation of the lesions, the onset of Hodgkin's disease should perhaps have been antedated by 6 months and the case not classified

as acute. However, the lumbar pain was of a constant and moderate character without definite localization, radiation or progression; thus, it was not typical of root pain and no lesions of the spine were found at autopsy.

Four weeks before the first apparent signs of Hodgkin's disease the same patient had an attack of herpes zoster lumbalis. Symptomatic herpes zoster is known to occur in cases of new growths and is also reported to occur during the course of Hodgkin's disease (12). A similar relationship cannot be precluded in this case; it should, however, be noted that the condition cleared up completely before the sudden onset of the manifestations of the main disease. Among numerous other diseases, herpes zoster has been reported as an initial sign of Hodgkin's disease (13). The possible etiologic or predisposing importance of preceding diseases is a matter of dispute. Against the theory of an etiologic relationship it can be argued that only in a minority of cases do the past histories reveal initial diseases (14); in addition, they are of an extremely varying character.

Signs of caries and dental abscesses preceded the onset of the disease in Case 2 in which rapid enlargement of the cervical lymph-glands was the first indication of malignancy. The onset of Hodgkin's disease has been ascribed to infection in the region of the head and neck and to chronic or recent upper respiratory tract diseases (3, 15); an association with dental infection has also been pointed out (13, 15). It has, however, been suggested that the association of Hodgkin's disease and upper respiratory diseases at the apparent onset of the former is due to the fact that when sufficiently obvious to be recognised, it predisposes to the development of a secondary infection of the upper respiratory tract (10). This may hold true for dental abscesses as well. If that be so, the rapid enlargement of the cervical glands in this case should be regarded as a sign of a fulminating terminal stage after a latent period of at least a year, with a hidden focus and no other signs than recurring dental abscesses. Although this possibility cannot be excluded it seems a little far-fetched. Furthermore, the clinical course points clearly to the cervical glands as being the primary site. Any possible etiologic significance of dental abscesses is probably as doubtful as that which one obtains in the case of herpes zoster.

Acute cases of Hodgkin's disease are characterized by a fulminating and usually feverish course of short duration; apart from this there are no typical clinical or laboratory findings. According to CHEVALLIER and BERNARD (4) visceral manifestations generally predominate in the acute cases although acute polyadenopathy is also seen; polynuclear leukocytosis is often present from the onset, but leukopenia is encountered in the more toxic forms (4). Death from a condition suggesting septicemia may

ensue although the immediate cause of death often depends upon the situation of the disease; thus, hepatic insufficiency is said to be a frequent factor (4).

The two cases reported had fulminating feverish courses of 5 and 8—9 weeks' duration, respectively. Typical Hodgkin's granulomatosis was only found in the lymph-glands and in the spleen; hepatic and myocardial damage as well as evidence of hydropericardium and pulmonary edema were striking visceral signs in both cases in one of which pleural effusion and glottic edema occurred. Leukocytosis was found in one of the cases. The immediate cause of death in Case 1 was not clear, while lymphatic obstruction and venous congestion caused the death of the second patient.

Attempts have been made to divide Hodgkin's disease into categories from its microscopic characteristics. JACKSON and PARKER (16) describe three types; the paragranuloma, the granuloma and the sarcoma. According to JACKSON's and PARKER's description our cases should be classified as Hodgkin's granulomatosis. The paragranuloma type is said to run a chronic course, while that of Hodgkin's granulomatosis is more variable. The sarcoma type is a more malignant form running a rapid course. However, transitional forms may occur, and the more benign forms may take on a malignant character. Furthermore, glands from the same individual may show all pathological variants (17). Hence, there is no pathological basis for a clinical division into acute and chronic forms.

It would appear that precise grading of the acute form of Hodgkin's disease, either from the past history of the individual case or from clinical, laboratory, autopsy, or even microscopic examinations, is not possible. The term »acute Hodgkin's disease» merely indicates a sudden onset and a rapid and lethal progression of the signs and symptoms of Hodgkin's disease.

SUMMARY

The difficulties in segregating acute Hodgkin's disease as a morbid entity are discussed and two illustrating cases reported.

ZUSAMMENFASSUNG

Die Schwierigkeiten, die Hodgkinsche Krankheit als pathologische Einheit abzugrenzen, werden diskutiert und zwei diese beleuchtende Fälle werden berichtet.

RÉSUMÉ

L'auteur examine les difficultés que l'on rencontre pour isoler en tant qu'entité morbide une maladie de Hodgkin aiguë et donne 2 cas en exemple.

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FROM THE MEDICAL DEPARTMENT (DIRECTOR: POUL KIRKETERP), MUNICIPAL HOSPITAL, HORSENS, DENMARK

SPECTACULAR EFFECT OF TESTOSTERON PROPIONATE ON MAMMARY CANCER METASTASES

Case Report

by

Poul Kirketerp

A woman, aged 65, was admitted to hospital on March 19, 1951. In 1946 she had been operated on for left-sided mammary cancer. She had received postoperative roentgen therapy and was well until January 1951, when she began to feel tired, became dyspneic, and lost weight. Pain in the back developed, and she noticed a large lump on the left anterior side of the chest.

Physical examination revealed an emaciated, weak woman with marked dyspnea at rest and coughing attacks on the slightest movement. On the left anterior surface of the chest, densely adherent to the skin and thoracic wall and extending from the second to the fifth ribs was a firm, nodular tumor, the size of a clenched fist.

There was dullness and impaired respiration in the lower posterior part of the lung and some edema of the left forearm and hand.

Chest roentgenograms showed a massive opacity, which occupied the lower two-thirds of the left lung and was densest towards the mediastinum. The signs appeared to be those of a growth — doubtlessly a metastasis. No signs of involvement in the ribs.

Roentgenograms of the thoracic and lumbar segments of the spine revealed extensive metastases and collapse of the bodies of the 6th, 7th, 8th, and 12th thoracic vertebrae.

The situation was complicated by the fact that the patient highly feared that her condition was a recurrence of cancer. She plainly told us that if we suggested roentgen treatment she would realize that it was cancer, and that she would then die of despair.

We decided to try a course of treatment with testosteron propionate (Perandren CIBA). From March 25, an intramuscular injection of 25 mg

Submitted for publication, Oct. 25, 1951.

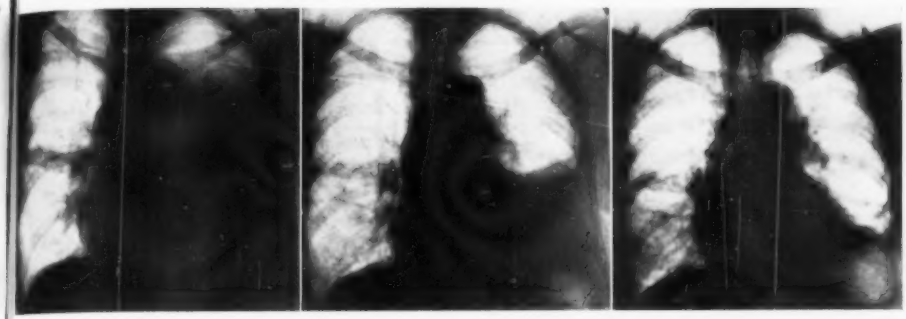

Fig. 1 a. Before treatment.

Fig. 1 b. 32 days after beginning of treatment.

Fig. 1 c. 73 days after beginning of treatment.

was given daily for 10 days, followed by 25 mg every second or third day until April 24, when a total of 15 injections had been given. At that time the pain and dyspnea had completely disappeared; the large tumor on the chest wall had diminished to a third of its original size, and there was a marked improvement both in the mental condition and general health.

The treatment was now supplemented by roentgen therapy, a total dose of 3,600 r being given to the spinal metastases. The tumor was not irradiated but had apparently completely disappeared on the patient's discharge on May 8.

The Perandren injections, 25 mg intramuscularly, were continued every fortnight and on the last follow-up examination (September 1) the patient had no symptoms whatever and looked very well.

The illustration shows the chest roentgenograms prior to the institution of treatment, after 32 days of treatment and after 73 days of treatment.

SUMMARY

A case report is presented of a woman with metastases which developed five years after radical mastectomy who was treated with testosteron propionate. The soft tissue secondaries completely disappeared. Smaller doses than usually recommended were used.

ZUSAMMENFASSUNG

Der Fall einer Frau mit Metastasen, welche 5 Jahre nach der radikalen Mammaamputation auftraten und mit Testeronpropionat behandelt worden sind, wird geschildert. Die Weichteilveränderungen verschwanden völlig. Geringere Dosen als gewöhnlich empfohlen werden sind angewendet worden.

RÉSUMÉ

Présentation du cas d'une femme chez qui des tumeurs métastatiques se sont développées cinq ans après la mastectomie radicale et qui a été traitée par le propionate de testostérone. Les tumeurs disparurent complètement. Les doses avaient été inférieures à celles qui sont généralement recommandées.

FROM THE RADIUM CENTRE FOR JUTLAND AND THE RADIOLOGICAL CLINIC (DIRECTOR: PROFESSOR CARL KREBS), THE MUNICIPAL HOSPITAL, AARHUS, DENMARK

PROBLEMS IN RADIATION MONITORING WITH FILM-BADGES

by

C. B. Madsen

The use of film badges for measurements of the irradiation received by the workers in radiologic clinics has become very common during the last decade. Normally, the films worn by the personnel are processed by standard methods together with calibration films, which have been exposed to known doses of radiation of varying amounts. The individual doses are found by comparing these two sets of films (1).

Several authors have found that the density of the exposed films is proportional to the dosage of roentgen rays received by the films (2, 3). It is also known that the density of the film also depends on the quality of the radiation and therefore the method gives the best results if both the calibration films and the measurement films have been exposed to the same quality of radiation. This is practically never the case. The wave length of the scattered radiation is longer than that of the direct beam, and in various types of roentgen therapy different filters are used: these effects give rise to radiation of varying quality. For example, it has been found that a density of 1.0 corresponds to 35 mr (milliroentgens) if the half-value layer is 0.7 mm Cu, and to 55 mr for a half-value layer of 1.3 mm Cu. If the calibration films are irradiated with a quality, the half-value layer of which is the mean value of these, one can only expect to be able to determine the dosage with an accuracy of $\pm$ 30 %. Since, in the first instance, it is sufficient to know whether the exposures are essentially larger, in the vicinity of, or smaller than the tolerance dose (fixed rather roughly), we have up to now used the film method in spite of its poor accuracy (4).

Submitted for publication, Sept. 21, 1951.
Aided by a grant from the Danish Anti-Cancer League.

The sensitivity of a photographic emulsion to gamma rays is usually about one tenth of its sensitivity to roentgen rays. Therefore, if the same member of the staff is exposed to both gamma and roentgen radiation, as is the case in this hospital, special care in the calibration procedure must be taken. The member might be required to change his film badge when he goes from one department to another although such a method is apt to give rise to mistakes.

It is believed that certain emulsions, reasonably independent of energy from about 0.05 to 2 Mev, are available. As yet, we have been unable to obtain such emulsions and have therefore attempted to increase the accuracy in another way.

In order to differentiate between the blackening caused by gamma and roentgen rays, part of the film is covered with lead, by which the roentgen rays are practically stopped, whereas the gamma rays are practically unimpeded and blacken the film. If a 1 mm sheet of lead is used, the fraction of gamma radiation passing through the lead is about 95 % ($\mu = 0.5$ cm^{-1}) of the incident rays. Normally, the hardest roentgen rays used have a half-value layer of 1.4 mm Cu; only a few per cent of these rays penetrate the lead.

Table 1

Densities of films exposed both to roentgen rays and to gamma rays

	0	200 mr	400 mr	800 mr
0	0	0.3	0.9	1.5
30 mr	1.0	1.3	1.8	2.5
80 mr	2.2	2.5	3.1	3.4
160 mr	3.4	3.8	> 4	> 4

Table 1 gives the densities of films irradiated (a) with roentgen rays only (2nd line), (b) with gamma rays only (2nd column), and (c) with different qualities of both kinds of radiation. The roentgen dose is given in the first column, the gamma ray dose in the first line. As long as the gradation curve is a straight line, the total densities are the sum of the densities caused by irradiation with gamma rays (2nd line) and roentgen rays (2nd column).

Accordingly, the dosage corresponding to a measurement film is found in the following way: — The density of the uncovered part of the film, D_1, and that of the part covered with lead, D_2, are found: the difference, $D_1 - D_2$, corresponds to the effect of the roentgen rays. By means of the density, D_2, the difference, $D_1 - D_2$, and the calibration curves of gamma and roentgen rays, respectively, the two doses are found.

The evaluation of the dose of the roentgen radiation will be more accurate if it is possible to determine the half-value layer of the latter. This is possible by covering the film with foil of different thicknesses (5).

The logarithms of the densities of the film behind the foils are plotted against the thicknesses of the foils themselves. The curve is normally a straight line, the slope of which gives the half-value layer. The small casette shown in figure 1 has been devised for the purpose. In both sides of the casette there are six quadrangular holes, which may be covered with squares of metal foil. The film is inserted into the casette, and two opposite holes, one on either side of the casette, are covered with the same kind of foil. For one pair of the holes, squares of 1 mm lead are used, while three other pairs are covered with squares of copper foil: 0.2, 0.5, and 1.0 mm thick, respectively. The last two pairs of holes are normally left uncovered. The half-value layer found in this way is in agreement with the half-value layer obtained by absorption measurements by means of an ionizing chamber.

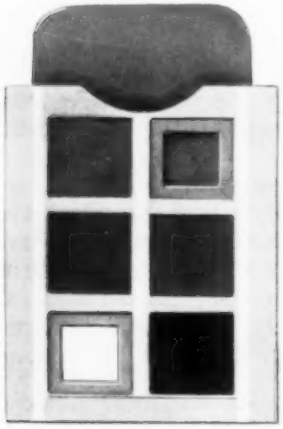

Fig. 1.
Casette for film-badges.

The curve is not, however, always a straight line. In the first place, if the film is irradiated with unfiltered roentgen rays, the beam is very heterogeneous and a straight line cannot be expected. In the second place, if the film is exposed to two (or more) different qualities of radiation, a complex curve will result; in such cases an attempt has been made to dissolve the curve into two straight lines corresponding to the quality of the radiations with which the calibration films have been irradiated.

If the film is also irradiated with gamma rays, the absorption of which in copper may be neglected, the density obtained behind the lead foil must be subtracted from the densities recorded behind the copper foils before the curve is drawn.

In this way it is possible to decide with which calibration curve — one for soft and the other for hard radiation — a measurement film must be compared in order to evaluate the dosage of roentgen irradiation. An effort has been made to measure the dose from films exposed to known quantities of both roentgen and gamma rays. The values found by the above-mentioned method agreed within 10—15 % with the known doses.

Thus, the errors of measurement may be decreased to at least one half although, on account of the uncertain fixation of the tolerance dose, this may not be of great significance. It is more important to be able to find out the kind of radiation to which the individual has been

exposed. When shortcomings in protective arrangements are disclosed, it is valuable to know in which department the unwanted irradiation has occurred.

SUMMARY

The author discusses the limitations of the film-badge method usually used in determining the amount of irradiation received by the personnel in radiologic departments and points out the variations, due to the quality of the radiation, which arise. A modification of the method, in which a special casette with metal foil filters is made use of, is described: greater accuracy and an estimation of the nature of the radiation, it is claimed, is thus obtained.

ZUSAMMENFASSUNG

Der Verf. bespricht die Begrenzung der Filmträgermethode, welche gewöhnlich zur Bestimmung der Bestrahlungsmengen benutzt wird, denen radiologisch tätige Personalgruppen ausgesetzt sind: die durch die Qualität der Strahlung bedingten Variationen werden hervorgehoben. Eine Modifikation der Methode unter Benutzung einer Spezialkassette mit Metallblattfiltern wird beschrieben: grössere Sicherheit wird so erhalten und eine Beurteilung der Strahlungszusammensetzung möglich.

RÉSUMÉ

L'auteur discute des limites de la méthode usuelle par laquelle on détermine la quantité de radiation à laquelle le personnel d'un service radiologique est exposé. Cette méthode qui comporte le port d'une pellicule témoin n'enregistre pas les variations dues à la qualité de la radiation. Une modification de la méthode est décrite. Il est fait usage d'une cassette contenant des feuilles métalliques filtrantes. On obtient ainsi une plus grande précision dans la mesure des doses et une indication sur la nature du rayonnement.

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FROM THE 2ND ROENTGEN DEPARTMENT (DIRECTOR: DOCENT W. MAGNUSSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

A DEVICE FOR THE PROTECTION OF THE TESTICLE IN ROENTGEN EXAMINATIONS OF ADJACENT ORGANS AND BONES

by

Wolfgang Magnusson

The effects of roentgen radiation on the testicles were first studied by ALBERS-SCHÖNBERG in 1903 and subsequently have been investigated by BERGONIÉ and TRIBONDEAU, REGAUD, SCHINZ and SLOTOPOLSKI and several others. We know that the less differentiated the cells of the seminiferous tubules of the testicle, the more sensitive they are to radiation. The mature spermatozoa are relatively resistant but the spermatogonia are so sensitive that a depopulation of the tubules can be brought about by a dose of 60 r. Doses of 200—300 r produce temporary castration and 500—600 r total castration. From investigations by MULLER and others on drosophila, we know also that radiation induces a high mutation rate which increases with the amount. So far, this effect has not been observed in mammals although the possibility of such an injury must be considered.

With the doses used in therapeutic work, safe protection of the testicles is necessary during the treatment of surrounding parts of the body. The amount of radiation received by the testicle in the roentgen examinations of adjacent organs and bones — for example in cystography, urethrography or radiography of the sacral bone — has generally been considered harmless and protection against it therefore unnecessary.

As far as I know, no detailed measurements of this radiation in various roentgen examinations have been published. The skin dose at the point at the shortest distance from the focus of the tube is measured with different exposures and from these observations the dosis in the testicles may be estimated to about 0.5—10 r — the lowest values in

Submitted for publication, Oct. 31, 1951.

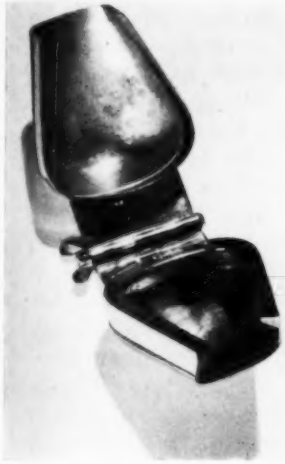

Fig. 1. Capsule, opened.

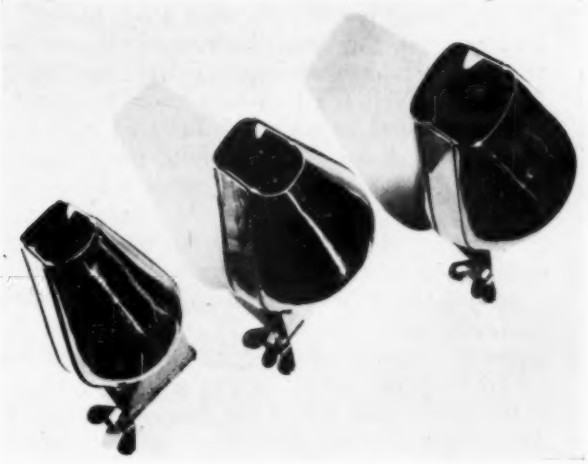

Fig. 2. Capsules of various sizes, closed.

Fig. 3 and 4. Capsules in urethrography.

the frontal and the highest in the lateral views of the surrounding tissues; in one examination doses up to about 30 r can be attained.

In such circumstances protection of the testicles seems to be desirable in examining non-sterile subjects if such protection can be arranged without any impairment of the result of the examination.

The usual protection with lead rubber, used in therapy and the lead capsule, long ago deviced by HOLZKNECHT for therapeutic work, are not suitable for diagnostic examinations, especially for the oblique and lateral views. I therefore asked a surgical instrument manufacturer to make metal capsules of different sizes in which the scrotum could be easily enclosed and which did not slip off when the patient changed position (Figs. 1 and 2). Most exposures may be made with these capsules without any impairment of the examination technique (Figs. 3 and 4). Preliminary measurements were made of the intensity of radiation on different points on the surface of the scrotum which was enclosed in a capsule of 1 mm of lead, covered with nickel-plated brass. These measurements, made by The Institute of Radiophysics in Stockholm, showed that the values around the neck of the capsule were about 10—20 times higher than in the middle portion and 20—40 times higher than at the base, where the doses in 6 exposures were as small as 0.02 r. As a result of these relatively high amounts of secondary radiation with low primary values and the experience that a heavy capsule is more difficult to secure in position, thinner capsules, made of 1½ mm o nickel-plated brass have been tried and new measurements carried out. In urethrography, without protection, the doses close to the testicle amounted on an average to 0.8 r per exposure. With protection, the doses in 6 exposures (64 kilovolts peak; 4-valve-apparatus; focus-skin-distance: 85 cm) in different parts of the capsule amounted to 0.01—0.08 r, the highest values being measured from points near its opening. The capsules thus shut out about 99 % of the radiation in such examinations.

These capsules will not fit small boys. A convex lead plate, secured with adhesive plaster, is preferable in such cases.

The capsules will be manufactured by the firm of Stille-Werner in Stockholm, Sweden.

For valuable help with the measurements I wish to express my gratitude to Mr. Lars Lorentzon, Engineer at the Institute of Radiophysics, Stockholm.

SUMMARY

The author describes a device for the protection of the testicle during the roentgen examination of adjacent organs and bones.

ZUSAMMENFASSUNG

Der Verfasser beschreibt eine Vorrichtung zum Schutz für die Hoden bei Röntgenuntersuchung von angrenzenden Organen und Knochen.

RÉSUMÉ

Description d'un appareil destiné à protéger les testicules au cours de la radio-radiographie des organes et des os adjacents.

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»STIPPLED EPIPHYSES» IN THE NEWBORN AND IN INFANTS

(Synonyms: Chondrodystrophia Calcificans Congenita, Dysplasia Epiphysialis Punctata)

by

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Although of not very frequent occurrence, irregular ossification of the epiphyses and apophyses (fragmentation, segmentation, punctation, mottling, and multiple ossification centres) is occasionally encountered in radiologic practice. Naturally, these changes will be most frequent in the age groups in which epiphyseal and apophyseal ossification centres appear and develop, *i. e.* in childhood and adolescence, but as the diseases which disturb the normal development of the epiphyseal centres usually cause a delayed appearance of these centres, irregular ossification may also be seen in older individuals up to the age of at least 40 to 50 years. These diseases are endocrine disturbances (such as myxedema, cretinism, pituitary dwarfism, and eunuchoidism), dystrophias (lipochondrodystrophy and chondrodystrophia Morquio), aseptic necroses in the epiphyses and a few others. There is no sharp lower age limit for the occurrence of irregular epiphyseal centres but owing to retardation they are scarcely encountered in individuals under the age of 2 years and are most common in somewhat older children.

On the other hand, densities in the epiphyses and apophyses may very occasionally be observed in the newborn and in infants at a time where normally no shadows of the epiphyseal cartilage are seen in the roentgenograms.

This disease was first described by CONRADI (1914), in a chondrodystrophic girl, aged 3 weeks, with shortening of the right lower ex-

Submitted for publication, Oct. 20, 1951.

tremity (3 cm), saddle nose, bilateral cataract, and peculiar epiphyseal densities.

In 1931 HÜNERMANN designated the disease chondrodystrophia calcificans congenita.

The first American report on the disease was published in 1924 by TISDALL & ERB. Of British investigators, FAIRBANK has shown particular interest in the disease. He designated the condition dysplasia epifysialis punctata and presented a survey of all cases on record, which at that time (1949) amounted to 16.

I have succeeded in finding reports of only 39 cases in the literature and I know of 3 unpublished cases. All these were reported under a variety of names: chondrodystrophia calcificans congenita, punctate epiphyseal dysplasia, calcinosis universalis (BLOXSOM & JOHNSTON), congenital deformities with stippled epiphyses and congenital cataract (LIGHTWOOD), chondroangiopathia calcaria seu punctata (HAYNES & WANGNER, COCCHI), and metaphyseal dyscrasia (LUND). Accordingly, it has been difficult to obtain a clear concept of the disease, particularly as certain investigators (MCCULLOUGH & SUTHERLAND, RESNICK) have published cases of entirely different disorders as epiphyseal dysplasia punctata. The cases reported by REILLY & SMYTH, BUXTON, SEARS, and WILKINS have nothing to do with epiphyseal dysplasia punctata, but several authors have erroneously considered them to be identical with this disease. The case described by BLATT et al. is one of chondrodystrophia calcificans congenita, although the cretinoid component is doubtful.

The only Scandinavian case was published by JORUP in 1944. In 1942, GRETE GØRTZ reported a case at a meeting of the Danish Pediatric Society. This is again reported below as case 3 (I am indebted to Professor OLUF ANDERSEN, of Queen Louise's Children's Hospital, and to Dr. GØRTZ for permission to publish this case).

Reports of Cases

Case 1. — P. N., a boy, born Dec. 11, 1946, was admitted to hospital the next day for deformities; death occurred a month later.

There was no family history of any conspicuous deformities; parents unrelated. Two years previously the mother had given birth to a full-term girl without deformities; no abortions. The second pregnancy was normal but birth somewhat premature; she had been given 10 cg ethyl phenylbarbituric acid daily for cryptogenic epilepsy; otherwise no medication, notably not cod-liver oil.

The weight at birth was 3,200 g; height 47 cm; cranial circumference 36.5 cm (normal 34 cm). On admission the patient was found to be a non-debilitated baby with normal skin color. The subcutaneous tissue was rather sparse. Skull: The anterior fontanelle was fairly large, 4 × 4 cm. The nose was broad, with a flat but not sunken bridge; no cataract; normal heart and lungs; small bilateral inguinal hernias; testicles undescended.

Fig. 1. Case 1. Flat broad nose; short flipper-like deformed upper extremities; short thighs.

All four extremities particularly proximally were deformed, short and plump; the deformities were essentially symmetrical. The left upper extremity was flipper-like. Both forearms were flexed at the elbow (left 90°, right 120°) and supinated. There was marked limitation of the movements of the shoulder and elbow joints; only rocking movements could be elicited in the left elbow. The skin was tense over the bones and muscles. Ulnar deviation of the hands; both hands were highly deformed with »main en trident». The thumbs were of almost normal length, the index and middle fingers short and plump, the ring finger strikingly long, and the little finger normal. The lower extremities were flexed at the hip and knee joints; passive movements were difficult to carry out owing to the apparent tightness of the skin over the joints. Bilateral talipes equinovarus, most pronounced on the right side; toes normal.

Roentgen examination: The skull was normal in size and shape, with somewhat large parietal foramina and a few Wormian bones at the posterior cranial fossa; no os tribasilare seen. The sella turcica was rather small. No prominence of the forehead and no retracted nose bridge. The bodies of C 3—7 and D 1—3 vertebrae were defective and separated into several parts; small calcifications were present in the place normally occupied by the coccyx. The remainder of the spinal column was normal. The thoracic skeleton was normal; no calcifications in the cartilaginous parts of the ribs. Heart: Normal. The pelvis was normal, apart from numerous small calcifications in the acetabula. The changes in the extremities were roughly equal on both sides; the humeri were short and rather plump; the metaphyses were not excavated but slightly increased in width. The bones of the forearm were shortened, the ulnae being shorter than the radii and markedly curved. At the site of the coracoid process and in the proximal humeral epiphysis there were numerous distinct, up to pinhead-sized, calcareous deposits (fig. 2); a few similar deposits were seen distally in the carpus. Only 4 metacarpal bones were present; that of the thumb was missing and had been replaced by a small calcareous deposit; the other metacarpals were deformed; the second, third, and fourth were club-shaped and tapered proximally. All the phalanges were present, but only the first and second phalanges of the ring finger and little finger were of normal shape, the others being more or less deformed. Small calcifications were seen in the epiphyses, especially of the three radial digits (fig. 3). The femur was short and somewhat broad, with rounded metaphyses; the fibula was considerably longer than the tibia, which was short and

Fig. 2. Case 1. Numerous distinct calcifications in the proximal humeral epiphysis and the coracoid process.

Fig. 3. Same case. Short curved bones of the forearm; tapered metacarpal bones, the first being replaced by a calcareous body.

increased in width; in the proximal and distal epiphyses of the femur and the tarsus numerous well-defined, in places slightly irregular, small dense calcifications were seen. The number of metatarsals and proximal phalanges was normal; the latter were slightly plump. The terminal phalanx of the great toe was present, but the second phalanges of the other toes were missing. The terminal phalanges of the second and third toes had been replaced by small calcareous deposits. There were no normal epiphyseal centres in the extremities.

Roentgen examination of the father, mother and sister did not reveal any abnormalities of joints.

Course: After three weeks in hospital, a large abscess of the right mamma developed and a few days later perforated spontaneously; another abscess developed in the region of the right elbow. The condition deteriorated and the infant died at an age of one month.

Autopsy: The following pertinent facts may be emphasized. The parietal foramina were large. The cranial bones were firm, and there was no tribasilar synosteosis; there was a small tentorial rupture on the left side. The thyroid gland was normal; weight 1 g. The thymus was small and defectively developed; weight 1 g. The bronchi of both lungs were diffusely dilated and could easily be opened right out to the surface of the lungs. The heart was somewhat large; apex broad; the ductus arteriosus was patent, with an opening of 2—3 mm and a longitudinal folding of the intima; the foramen ovale was closed by a valve, but a small aperture, 2—3 mm wide, persisted; in the fibrous part of the interventricular septum there was a defect measuring 5—6 mm; the myocardium was firm and there were no valve changes.

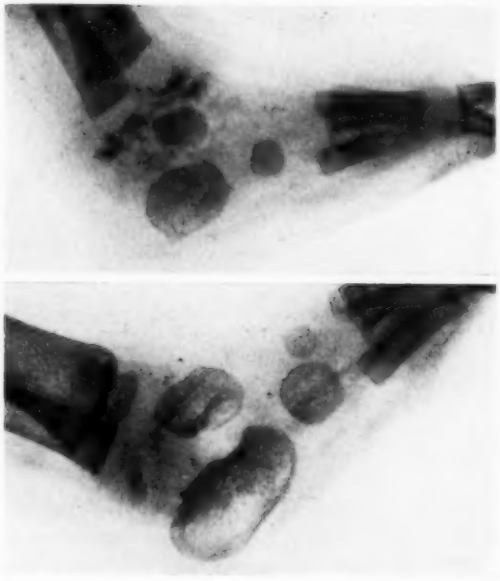
The histological examination of the bones showed the same picture as described by Conradi and Kwerch.

Fig. 4. Case 2. Cloudy densities in the head of the left femur.

Case 2. — J. E., a girl, aged 2½ months, was admitted to hospital for one week by reason of paralysis of the right upper and the left lower extremities, vomiting, and failure to thrive.

The parents were cousins. There was no family history of short extremities or deformities of hands or feet. The patient was the younger of two children. The first child, aged 5 years, had always been in good health. During her second pregnancy the mother had albuminuria for three months, but otherwise the pregnancy had been normal; had been given 250 calcium tablets of 0.5 g and 250 g cod-liver oil during pregnancy; the birth occurred three weeks before term: the baby was considered mongoloid; weight at birth 3,000 g; length 48 cm. During the first month of life the infant throve well, but then began to vomit and failed to gain. When the infant was 7 weeks old, the mother noticed that the right wrist was flaccid and the left lower extremity could not be extended. Only during the first days in hospital did the patient vomit a little but after discharge occasional vomiting returned.

Cond. on adm.: The general appearance was that of a 2½-month-old, fairly well-ourished girl. Weight 4,000 g (normal weight for height 3,800 g); height 53½ cm (normal 60 cm), cranial circumference 37 cm. The bregma—iliac crest and the iliac crest—heel measurements were equal. The patient was able to fix her attention for short periods but could not smile. The skull was firm: the anterior fontanelle measured 3½ × 3½ cm. The bridge of the nose was broad, flat but not retracted. There was a very slight epicanthus: no cataract: no signs of cardiac disease. Extremities: The right arm was moved less then the left: the child gave the impression of having tenderness and cried when passive abduction of the right shoulder joint was attempted. The right upper arm seemed to be ½ cm shorter than the left. The left lower extremity was held semiflexed at the hip and knee joints, and owing to resistance (myogenic contracture) extension was difficult. Owing to shortening of the left femur, there was an inequality in length of the lower extren.ities of 1½ cm. Slight valgus position of the left foot. Temperature: normal. Urine: normal. W. R.: negative; blood urea 40 mg%: serum calcium 10.6 mg%;



a.

b.

Fig. 5. Case 2. a) Three normal centres and calcifications in the proximal parts of the tarsus (Feb. 1950); b) The calcifications have decreased considerably (Feb. 1951).

serum phosphorus 3.5 mg%; serum phosphatase 170 units (LUNDSTEEN and VERMEHREN).

Roentgen examination: The cranial bones were somewhat thin; no retracted nose bridge; no stippling of the base and no os tribasilare. Spinal column, thorax and ribs: normal; no signs of cardiac disease. Extremities: There were faint cloudy opacities in the head of the right humerus (perhaps also in the left) and in the proximal epiphysis of the left femur (fig. 4) and more distinct, granulated densities in the carpus and tarsus on both sides. Ossification centres: small centre in the head of the humerus but none in elbow or hip joints. Normal ossification centres in the distal end of the femur and the proximal end of the tibia. There were three centres in the tarsus (fig. 5 a), whereas none were definitely observable in the carpus. The metaphyses and diaphyses were normal, without signs of chondrodystrophia; yet the left femur was shorter than its fellow.

The patient was discharged (20. 3. 50). The mother was advised to carry out daily passive extensions of the left lower extremity in order to bring about some improvement of the contracture; ascorbic acid and vitamins A and D were prescribed.

Further examination (13. 2. 51), when the patient was 13½ months old; length 70 cm (normal 74 cm); weight 8,540 g; cranial circumference 46 cm; Hb. 95 %. During November—December 1950, the child had been admitted to an orthopedic hospital where a plaster cast extending from the umbilicus to the toes was applied; it could now sit up,

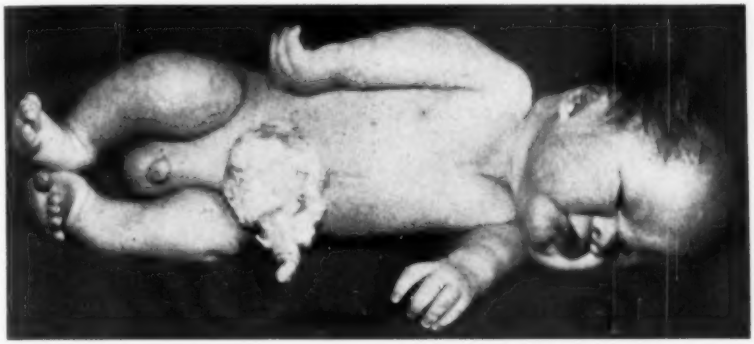


Fig. 6. Case 3. Saddle nose, bayonet-like ankle joints.

but did not attempt to stand; it could grasp objects but had no strength in the arms; the patient could say a few words.

Physical examination revealed slight hypertelorism and epicanthus. The anterior fontanelle measured 3 × 2 cm. The child had cut the medial incisors in both jaws. The right arm could be moved unimpededly and no definite shortening was present. The left lower extremity was held slightly flexed at the hip joint, but could be extended without difficulty; was 1.5 cm shorter than its fellow and slightly thinner; slight pedes plani.

Roentgen examination: Chest: Normal. Both shoulder joints: The calcifications in the proximal humeral epiphyses had decreased, especially on the right side; the ossification centres were bean-sized, the left slightly larger than the right. Pelvis: The calcifications in the epiphyseal cartilage of the left femur were barely visible; a hazelnut-sized ossification centre was visible on the left side; it was slightly larger on the right. Hands: The calcifications had almost completely disappeared, only a few small indistinct scattered granules persisting. There were two ossification centres, each the size of half a pea, in each wrist. Ankles: The calcifications in both tarsi had further decreased. There were four normal ossification centres (fig. 5 b).

Case 3 (Dr. Gortz's case). — J. H., a boy, born on Oct. 17, 1942, was admitted to hospital the following day. Death occurred three weeks later.

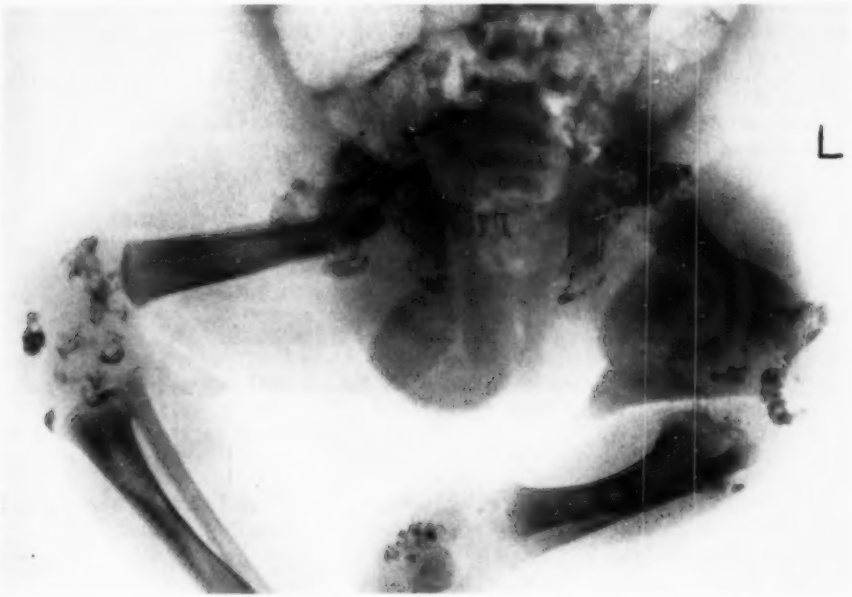
No family history of dwarfism. The patient was the younger of two children; his brother, aged 3, was alive and well. The mother had had no abortions and the last pregnancy was normal; had been given calcium but not cod-liver oil during pregnancy.

The child was born at full term. Weight at birth 3,000 g; length 41 cm. The general condition of the patient was poor; was cyanotic, and very cool to touch; temperature 33° C; whimpered a little, but the cry was otherwise moderately strong. Broad saddle nose (fig. 6). Bilateral cataract; the left lens translucent peripherally; the right lens dense, gray, completely opaque. Heart and lungs: normal. Testicles undescended. The extremities were short, notably the femora and humeri; the hands rather large and plump with typical »main en trident». The legs were markedly curved with bayonet-like ankle joints and in a valgus position, particularly on the left side. The right humerus measured 5 cm, the left $4^1/_2$ cm; the right femur was $5^1/_2$ cm, the left 6 cm. The inequality in length was probably due to fractures (see later). There was incomplete extension

Fig. 7. Case 3. Segmented vertebral bodies; stippling of the sternum.

of the elbow joints, and the knee joints were flexed 60° and could not be extended. The ankles could be plantarflexed to right angles only. The patient fed poorly; there was diuresis (30—100 ml per 24 hours); an occasional slight quivering of the arms and jaw but no actual cramps observed; Chvostek positive on one occasion; Trousseau and Erb negative. On the twelfth day of life the child developed macroscopic hematuria, and the next day there was slight bleeding from the umbilicus, for which reason vitamin K (Soluchinon, 5 mg daily) was given for 4 days, after which time the bleeding ceased. Four days before death occurred, a walnut-sized soft fluctuating intumescence, probably a hematoma, was felt in the occipital region. B. C.: Hb. 96 %, erythrocytes 5,300,000, leukocytes 9,360, thrombocytes 460,000. Serum calcium 9.8 mg%, serum phosphorus 5.6 mg%, serum phosphatase 224 units (not fasting).

(Mother's serum calcium 11 mg%, serum phosphorus 4.1 mg%, serum phosphatase 102 units; W. R. negative.)



ig. 8. Case 3. Numerous highly irregular densities in the epiphyses and apophyses (note right patella); fracture of the right femur.

Fig. 9. Fig. 10.

Fig. 9. Case 3. A very dense calcification corresponding to the calcaneal apophysis.
Fig. 10. Same case. Hourglass-shaped pattern in the metacarpal bones.

Roentgen examination: On admission the skull appeared to be of normal size and the cranial bones of normal thickness; distinct saddle nose and marked prominence of the frontal and parietal bones; no intracranial calcifications; indefinite signs of any os

tribasilare; no stippling of the base. Further roentgen examination the day before death revealed a soft-part shadow over the occipital bone but there were no bone defects. Lungs and heart: normal. The skeletal system showed typical chondrodystrophic changes (fig. 8), notably in the humeri, femora, tibiae, and fibulae, which were all short and plump with metaphyses increased in width and excavated. The proximal end of the fibulae reached higher than the tibiae; the radii and ulnae were of the same length. The phalanges of the fingers were rather thickened; in the proximal phalanges and particularly in the metacarpals a peculiar hourglass-shaped pattern was seen (fig. 10). Furthermore, numerous irregular dense calcifications were present throughout the cartilage of the epiphyses of the long bones, along the spinal column (most pronounced in the upper part of the thoracic and whole of the the cervical segment), in the lateral mass of the sacrum, acetabulum, sternum, in the apophyses (the inferior angle of the scapula, acromion, coracoid process, tuber ischii, and tuber calcanei), and in the carpi and tarsi (figs. 9 and 10). The vertebral bodies were distinctly separated into anterior and posterior portions. Both hip-joints were subluxated. On admission a transverse fracture of the left humerus and a spiral fracture of the right femur were found; just before death distinct callus formation was observed. Two normal ossification centres were present in each tarsus and possibly one in the shoulder joint but none in the knee, hip, elbow, or wrist joints. No deformities of toes or fingers, except for the short phalanges. Calcifications similar to those found in the bones were seen in the laryngeal cartilages.

Autopsy was not permitted.

Roentgen examination of the elder brother did not reveal any epiphyseal abnormalities.

Discussion

Clinical Picture

The clinical picture is highly variable, and superficially it may be difficult to group these cases under the same entity and obtain a clear impression of the characteristics of the disease. However, after a review of all the cases available I find that it is possible to enumerate five signs, which are so frequently encountered that they may be said to constitute a typical picture. Usually at least three of these signs are observed in the patients; in exceptional cases found only by examination of relatives the sign which is of decisive importance in the diagnosis, viz. stippled epiphyses, is detected.

These five signs are:

(1) *Micromelia and rhizomelia.* In the majority of cases more or less pronounced shortening of the extremities, essentially due to a decrease in the length of the humeri and femora, is present, whereas the peripheral bones are generally of normal length. Owing to the short lower extremities the patients are dwarfs, in pronounced cases with a distinct chondrodystrophic configuration. The upper extremities in these patients may be markedly shortened, sometimes flipper-like (phocomelia, fig. 1). In milder cases the micromelia and rhizomelia are less pronounced and normal proportions are usually found in patients who may be examined because of the presence of stippled epiphyses in a brother or sister. In

some cases the development has been followed over a number of years. It then appears that the proportion between the length of the trunk and that of the extremities approaches normal, although the patient can scarcely ever be expected to reach average height; a development in the opposite direction may, however, also be encountered (BURCKHARDT).

(2) *An additional shortening of 1—4 cm in one or, possibly, two extremities* was reported in the literature to be present in almost half the cases. This shortening is also usually caused by the condition of the humeri and femora. During the growth of the child the shortening persists in such a way that the limb remains about 1—4 cm shorter than its fellow, and in none of the available cases was it possible to demonstrate development approaching normal. In a few cases the absolute shortening increased to 8—9 cm (MARQUARDT and MIESCHER).

(3) *Semiflexion and limitation of extension of the larger joints.* In many cases some of the larger joints (elbow, shoulder, hip, knee, and ankle joints) were held semiflexed, and limitation of movements was present; notably extension may be difficult, and passive movements meet with a strong elastic resistance. In other cases only rocking movements of the joints may be carried out. The semiflexed position and the limitation of extension may be caused by changes in the ends of the epiphyses but are usually due to changes in the soft parts, either shortening of the muscles by the formation of connective tissue (LUND) or tight joint capsules or integuments. Owing to the changes in the muscles, joint capsules and skin and to the increased width of the metaphyses, the joints will in these cases appear relatively swollen. The limitation of movement in the contractures will be most pronounced in the extremities with the greatest shortening but may also be seen in extremities of normal length. Little experience is available as to the further course of these para-articular contractures.

(4) *Bilateral congenital cataract* was mentioned in nine out of 42 patients. In most cases, the visual defect was observed early; in one instance, however, it was not noticed until the patient was about 12 months old. In several cases this sign probably escaped notice.

(5) *Stippled epiphyses.* This change will be discussed in detail under the description of the roentgenologic signs.

Other clinical findings: The skull is usually of normal size; of the cases on record, it was somewhat enlarged in three and smaller than normal in two instances. The most frequent and most characteristic changes are found around the bridge of the nose. In eleven reported cases it was retracted, and in seven it was broad and flat but not retracted. In nine cases the fontanelles were reported to be large. The

neck is often short owing to disturbances in the ossification of the cervical spine. The trunk shows normal proportions. In six instances congenital cardiac disease was observed. Generally, the ductus arteriosus is patent or a septal defect present. Sudden heart failure encountered in five cases in which no preceding cardiac disease had been diagnosed was supposedly due to a congenital defect.

There are no intra-abdominal changes. Umbilical and inguinal hernias as well as undescended testes are mentioned in the literature. — In addition to the previously mentioned abnormalities of the extremities, there is an increased incidence of the following conditions: adactylia, hypodactylia, and syndactylia; varus or valgus position of the hip, knee, and ankle joints; luxations, notably of the hip joints; and ulnar deviation of the wrist.

In several cases skin changes are encountered. Some authors report a dry, scaly skin; in one case there was dermatitis exfoliativa Ritter (Burckhardt) and in another, ichthyosis sebacea (Vychytil); in two cases follicular atrophoderma was observed (Curth, Miescher); Hässler & Schallock mentioned a patient with feather-like changes of the skin.

Blood examinations: In 17 of the cases on record, a W. R. was carried out; it was negative in all instances. The serum calcium and phosphorus were determined in 15 cases; in 12, normal values were found; of the remaining 3, the serum calcium was increased in 2 and decreased in 1 at the first examination, but shortly afterwards the values returned to normal. The serum phosphatase was determined in 10 patients; it was normal in 9 and highly increased in the remaining somewhat atypical case (Borovsky & Arendt).

The birth weight is usually subnormal (2,500—3,000 g), and one half of the infants were born before term.

In six cases, the authors expressed the view that the infants were mentally retarded. Mental retardation is most frequently combined with deformities and cataract.

Roentgenologic signs

The roentgenologic changes are of decisive importance in the diagnosis. Most frequently, these occur in the extremities, notably those affected by shortening or deformity. If marked changes are present in the extremities, they will generally also be found in the spinal column, sternum, and cranial parts preformed in cartilage. Extremities: Densities occur in varying form, size and number in the epiphyseal and apophyseal cartilages and in the carpi and tarsi; they occupy a greater or smaller part of these cartilages and appear either before or simultaneously with the development of the ossification centres, but are localized more peripherally.

These densities (stippling) may be of various types:

(1) Single scattered well-defined rather regular densities (fig. 10) simulating ossification centres.

(2) Numerous, larger or smaller, often highly irregular densities occupying the greater part of the epiphysis (fig. 8), possibly surrounding a central ossification centre as previously mentioned.

(3) Cloudy densities occupying more or less of the cartilage (fig. 4).

In milder cases, stippling is present only in a few epiphyses. In otherwise normally proportioned patients with shortness of one extremity, stippling may be present only in the epiphyses of that extremity; in other cases it may also be seen in the epiphyses of the fellow extremity. The stippling usually increases in extent and irregularity with the deformity of the extremities (cf. fig. 4 and fig. 8). The actual ossification centres are independent of these densities. In epiphyses where there are no densities, the ossification centres usually appear at normal times; on the other hand, in the presence of stippling there may be some delay in the development of the ossification centres.

In agreement with the clinical picture, the long bones, particularly proximally, in severe cases are short and show an increase in the width of the metaphyses, although typical chondrodystrophic changes with excavated metaphyses are not seen in all cases; most frequently, the metaphyses are rounded.

Usually, the skull does not exhibit any characteristic changes. The size and the condition of the bridge of the nose have already been mentioned. In some cases where it is also found in other bones, the stippling may involve parts of the base of the skull preformed in cartilage, just as in the epiphyses. In the spinal column the changes are essentially confined to the cervical segment and the upper part of the thoracic segment, but in pronounced cases they may extend further downwards. The changes take the form of a varying number of dense spots, arranged segmentally both in the vertebral bodies and processes.

Some authors (HILLIARD, MAITLAND) have mentioned a cruciform segmentation of the bodies suggesting persistence of the notochord.

In the soft parts of the neck, densities may be seen in the hyoid bone and the laryngeal and tracheal cartilages. In the thorax stippling may occur in the sternum (fig. 7) and in the ribs posteriorly. In the pelvis the stippling is most distinct in the ala of the sacrum and the region around the acetabulum. In the presence of cardiac disease the heart may be enlarged and changed in form. The legs may be curved with the convexity anteriorly or laterally. In some cases, the radius and fibula extend proximally to the ulna and tibia, respectively, as is the case in chondrodystrophia. The deformities of the hands do not

present any characteristic features; an example is seen in figure 3. Spontaneous fractures have not been mentioned in the literature, but were seen in case 3 reported in this study. In two patients there were triangular densities with the bases towards the metaphyses and the vertices pointing towards each other in the diaphyses. HILLIARD reported such densities in the metacarpals, tibiae and fibulae, and in case 3 reported above they were present in the metacarpals. A vertical density in the middle of the symphysis was occasionally seen, and in some cases early calcification of the apophysis of the calcaneus was reported (fig. 9).

Development of the bones during growth: Usually, the diaphyses become somewhat longer and slimmer, while the metaphyses continue to be rather plump. If there are typical chondrodystrophic changes, the development will correspond to that seen in chondrodystrophia.

In the cases where the stippling was followed, it subsided in the course of the first years of life, so that it could not be distinguished at the age of $3^1/_2$—4 years. The densities may disappear in two different ways:

(1) They may either be slowly resorbed (fig. 5 a and fig. 5 b) (HÜNERMANN), or

(2) they are gradually incorporated in the normal ossification centre during its growth, so that usually significant changes in the bony structure cannot later be distinguished; temporarily the ossification centre may be mulberry-like (BURCKHARDT).

When the stippling has disappeared, it is not possible to diagnose the disease as an independent entity. The patients will be looked upon as being chondrodystrophic, normally proportioned with one short extremity (possibly unilateral chondrodystrophia), or as being completely normal.

The reason for the first medical examination was deformities in nine cases, infection in six, failure to thrive in four, one short leg in four, cardiac disease in one, bilateral talipes calcaneovarus in one, and nutritional disturbances in two cases. Five cases were disclosed by family examinations, and in ten cases no reason for the first medical examination was stated.

Prognosis

Children with marked deformities, possibly complicated by cataract and cardiac disease, die at a young age. Thus, at least 16 of the 42 patients died young. Of these, 15 succumbed within the first year of life, and the last died at the age of $3^1/_2$ years. Five of the 16 patients died of pneumonia, five of other infectious diseases, four of cardiac

failure, and two of unknown causes. The prognosis for restitution has already been discussed.

Differential Diagnosis

The differential diagnosis does not present any difficulties. The clinical picture is most frequently characteristic. Special attention should be directed to shortness of one or two extremities, contractures, and cataract. The roentgenologic changes in the epiphyses and apophyses are so characteristic as regards time of occurrence and appearance that they cannot be mistaken for signs of other diseases.

Etiology and Pathogenesis

The etiology and pathogenesis are unknown. There is no evidence indicating hypervitaminosis A or D, or hypothyroidism. Histological examinations suggest chondrodystrophia (all cases examined had, however, marked deformities). In addition, the calcifications, the rather frequent occurrence of cataract and the course of the disease may be indicative of possible transitory changes in the calcium metabolism in mother or child.

From the cases in the literature it cannot be decided whether the condition is hereditary (CURTH), but its familial incidence cannot be ignored. HAGNES & WANGNER, MAITLAND, and VINKE & DUFFY each reported two cases in siblings, and in a sibship of four, RAAP found changes in all the members.

Treatment

Causal therapy is out of the question as the etiology is unknown, and symptomatic treatment will bring about only slight improvement in the condition. As in the case of chondrodystrophia proper, the micromelia and rhizomelia must be regarded as irresponsive to treatment; possibly orthopedic correction of a unilateral short lower extremity may be necessary. In none of the cases on record did the cataract require treatment. Therapy should principally be aimed at the myogenic and dermatogenic contractures, and here orthopedic surgery will be appropriate. Isolated subluxation or a valgus or varus position should also be corrected. If the condition is combined with other anomalies, the prognosis for life is so grave that therapy is unnecessary. The infections, which are the most common cause of death, should be combated in the usual way. Death due to cardiac disease cannot be prevented. Owing to the other deformities, operative measures for the cardiac condition can scarcely be considered.

SUMMARY

On the basis of 39 cases from the literature and three of the author's cases of stippled epiphyses in the newborn and in infants a description of the clinical and roentgenologic picture is presented. Five signs are emphasized: (1) micromelia and rhizomelia, (2) additional shortness of one or two extremities, (3) semiflexion and limitation of extension of the larger joints, (4) bilateral congenital cataract, and (5) stippled epiphyses. The condition has been found in infants and children up to the age of 3—4 years. Most cases must be considered to be a form of chondrodystrophia, possibly associated with disturbances in the calcium metabolism in mother or child.

ZUSAMMENFASSUNG

Auf Grund von 39 aus der Literatur gesammelten und 3 eigenen Fällen von punktierten Epiphysen bei Neugeborenen und Kleinkindern wird das klinische und röntgenologische Bild beschrieben. Fünf Symptome werden hervorgehoben: 1. Mikromelie und Rhizomelie. 2. Zusätzliche Kürze einer oder beider Extremitäten. 3. Semiflexion und Einschränkung der Extension der grossen Gelenke. 4. Doppelseitiger kongenitaler Katarakt und 5. Punktierte Epiphysen. Dieser Zustand wurde bei Neugeborenen und Kleinkindern bis zum 3.—4. Lebensjahre gefunden. Die Mehrzahl der Fälle muss als eine Art von Chondrodystrophie betrachtet werden, möglicherweise verbunden mit Störungen des Calciumstoffwechsels der Mutter oder des Kindes.

RÉSUMÉ

En se basant sur 39 cas décrits dans la littérature et sur trois cas découverts par lui, l'auteur donne une description des tableaux clinique et radiologique qui accompagnent les ponctuations épiphysaires chez le nouveau-né et chez les jeunes enfants. Il insiste sur cinq signes: (1) micromélie et rhizomélie, (2) de plus, raccourcissement d'un membre ou de deux, (3) demi-flexion et limitation de l'extension dans les grandes articulations, (4) cataracte congénitale bilatérale et (5) épiphyses ponctuées. Ces anomalies ont été relevés chez des enfants de moins de 4 ans. La plupart des cas sont considérés comme étant des chondrodystrophies accompagnées peut-être de troubles du métabolisme calcique chez la mère ou chez l'enfant.

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FROM THE ST. GEORGE'S COURT COLLECTION OF LEPROUS SKELETONS, NÆSTVED (TRUSTEE: DR. VILH. MØLLER-CHRISTENSEN, ROSKILDE) AND DEPARTMENT OF RADIOLOGY (DIRECTOR: DR. BORGE FABER), COUNTY HOSPITAL, NÆSTVED, DENMARK

LEPROUS CHANGES IN A MATERIAL OF MEDIÆVAL SKELETONS FROM THE ST. GEORGE'S COURT, NÆSTVED

by

Vilh. Møller-Christensen and *Borge Faber*

Leprosy, which to-day counts 5 or 6 millions as its victims, may be traced as far back as ancient civilization. Owing to its special character, leprosy has been considered one of the oldest and most severe scourges that ever afflicted humanity.

Among the old civilized nations of the East and in mediaeval society leprosy was regarded as a dangerous and incurable infectious disease, and lepers were therefore treated as outcasts, excluded from the company of their friends and family and banished to spend their lives in deserts or uninhabited waste places; or they were interned in St. George's Courts.

The present skeletal material is derived from such a reservation — the St. George's Court in Aaderup near Næstved. The first account of this reservation is from 1261. It fell into disuse in 1542 like the other leper courts in Denmark. During the 300 years of their existence their mission had been so well fulfilled that leprosy in Denmark had been virtually exterminated. The skeletons found, therefore, are no doubt from the period 1260 to 1542.

Previous workers have dealt mainly with the clinical features, spread, and means of combating leprosy, but during recent years radiologists have displayed interest in the bony changes caused by the disease. Since these changes, affecting particularly the hands and feet, are extremely characteristic, it is reasonable to endeavour to trace the history of leprosy from paleopathological findings.

Submitted for publication, Oct. 31, 1951.

Fig. 1. St. George's Churchyard, Næstved. The skeletons are completely and carefully freed of the overlying earth before being exhumed. This is the only way of making sure that even the smallest bones are collected and of avoiding the mixing of the bones of the various skeletons.

Despite the immense material of human skeletons and mummies from pre-historic and historic times, the earliest case of leprosy so far demonstrated, is no older than A. D. 600. The mummy in question, in which lepra mutilans is claimed to have been diagnosed, is that of a Copt.

Skeletal studies from Danish mediaeval churchyards had up to 1948 divulged only two cases of leprosy — in an elderly woman from the Øm Abbey and in a younger woman from the Æbelholt Abbey.

During excavations of the St. George Church at Åhus near Lund in 1946, the Swedish archaeologist MATS PETERSSON exhumed a number of skeletons in at least one of which leprous changes are said to have been detected.

Up to 1948 the Coptic mummy of about A. D. 600 and these three Scandinavian leprous skeletons formed the only material for comparing present-day leprosy with that of olden times and for studying the interesting question as to whether leprosy had changed in character in the course of time.

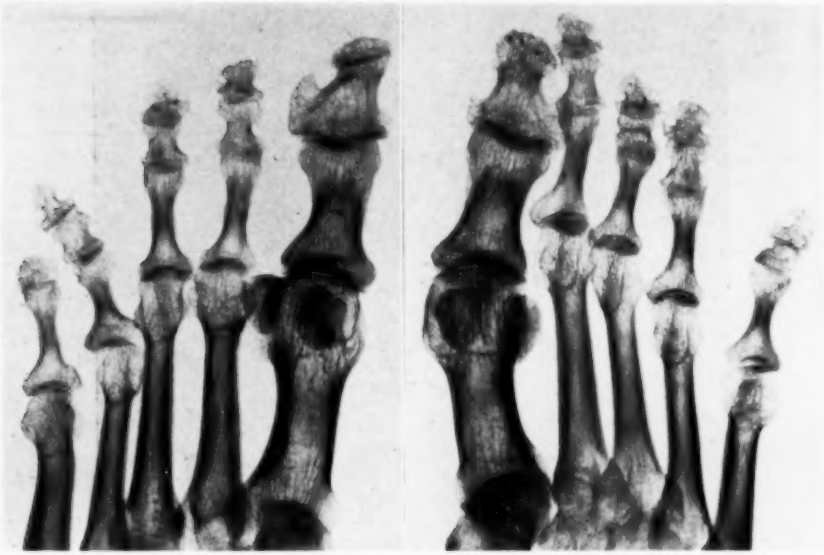


Fig. 2. Initial leprous changes characterized by flattening of the cancellous tuft and minute nicks.

Fig. 3. Moderate leprous changes characterized by atrophy and loss of the phalanges and concentric atrophy of the metatarsals.

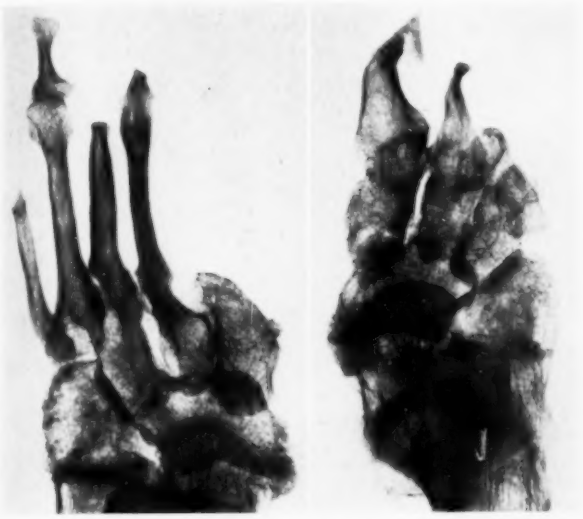


Fig. 4. Severe leprous changes. The toes of the left foot have atrophied and disappeared. The metatarsals of the right foot have also been lost; the tarsal bones are still relatively intact.

Fig. 5. Severe leprous changes involving loss of the tarsal bones (first and second cuneiform and cuboid bones).

In 1948, one of us (VILH. MOLLER-CHRISTENSEN), found the St. George's Court of Næstved which, as mentioned above, had been in use from about 1260 to about 1540. In 1950 and 1951 he conducted comprehensive excavations of the churchyard belonging to this reservation and exhumed about 200 skeletons, more than half of which bore the unmistakable marks of leprosy.

The reason why this unique discovery could be made at all was, that unlike the majority of the Danish St. George's Courts, the one in Næstved had not been disturbed by subsequent burials or in other ways made unfit for skeleto-archaeological studies. Since we now have access to a large material of skeletons, showing leprous changes, from mediaeval Denmark, this paper is devoted to a comparison of the skeletons from Næstved with radiological publications on present-day lepers.

Osseous changes in leprosy in a large clinical series have been described in great detail by JAMES BARNETSON in this journal. In early cases (duration of signs 1—20 years) he found changes confined to the distal margins of the terminal phalanges. The changes first consisted of minute nicks which grew larger, followed by loss of outline and fraying of the cancellous

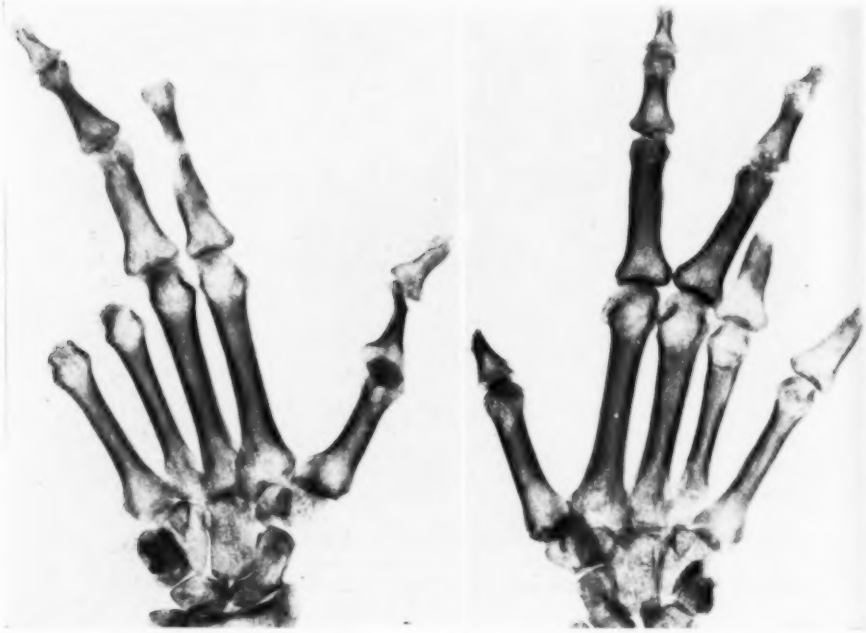


Fig. 6. Moderate leprous changes involving atrophy and loss of phalanges.

tufts. Later, the tufts grew atrophic, the distal margins flattened, and if the lateral margins were involved, »sliced-off» appearances resulted. With further progress the tufts disappeared and the shafts became frayed and notched with a »sliced-off» margin; lastly, only the bases of the phalanges remained as flat discs which eventually disappeared; the same process was then continued in the more proximal bones. In advanced cases (duration of signs from 2 to 33 years) the principal lesion was the continuation of the atrophy proximally, while periosteal reaction, osteosclerosis, and sequestrum formation were rare in the absence of secondary infection. Atrophy proceeded slowly until the phalanges were completely absorbed, the process being then repeated in the more proximal bones until whole digits disappeared. Metatarsal bones were frequently but metacarpals rarely affected. Involvement of tarsal bones was uncommon and there were no cases showing atrophy of carpal bones.

Numerous cases were characterized by slight atrophy of the distal phalanges and gross destruction occurred more proximally in bone surfaces adjacent to interphalangeal or metacarpo-phalangeal joints and was associated with flexion deformities.

Fig. 7. Example of non-specific, secondary inflammatory destruction adjacent to the third metacarpo-phalangeal joint exposed to injury because of contracture.

Gross destruction of the proximal bones of the feet was occasionally due to secondary infection.

Lesions in advanced cases were always bilateral, but rarely symmetrical. »Concentric atrophy», *i. e.* gradual narrowing of the shaft of a long bone was seen in proximal phalanges, metatarsals, and metacarpals, but never in distal phalanges. In concentric atrophy dense cortical bone still remains visible in cases in which the shaft has become needle-like.

A summary pathological investigation of the material from Næstved showed that the skeletons exhibited extremely characteristic changes of leprosy in the bones of the skull, hands, legs and feet. In this respect the skeletal material differed markedly from the large collections of skeletons from Æbelholt and Øm Abbeys in which leprous changes were found in but one skeleton from each churchyard.

The osseous changes corresponded to those described by BARNETSON, and consisted mainly of widespread atrophy of the bones, most marked in the distal parts; local destructions and new bone formation due to secondary infections were more uncommon.

Fig. 8. Example of non-specific, secondary inflammatory changes leading to new bone formation and fusion of the metatarsal bones.

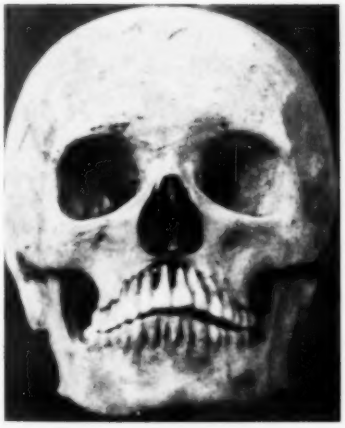
Slight changes with minute nicks and flattening of the cancellous tuft are shown in Fig. 2; the atrophy has not yet affected the more proximal bones. Fig. 3 shows marked atrophy of the toes and metatarsals. The atrophy is manifest partly as a disappearance of the distal portions of the bones and partly as concentric atrophy causing narrowing of the shaft, while the cortical bone is preserved.

Fig. 4 shows progression of the atrophy and destruction of the metatarsals and Fig. 5 marked atrophy; the tarsal bones have become necrosed.

In Fig. 6, the atrophic changes are seen to affect mainly the fingers.

Non-specific, secondary changes of an inflammatory nature in the form of local areas of destruction adjacent to the metacarpophalangeal joints are seen in Fig. 7. They may be explained by these sites having been exposed to injury by contractures. Non-specific, secondary new bone formation — periosteal reaction due to secondary infection — is illustrated in Fig. 8; the foot must have been particularly exposed to secondary infection; owing to contraction, it has been held in the varus position, so that the patient walked on the lateral margin of the foot; the tuber calcanei is so markedly »worn» that it must be presumed that the patient walked on the exposed bone.

Fig. 9. Facies leprosa showing atrophy of the area adjacent to the nasal opening and complete disappearance of the anterior nasal spine.



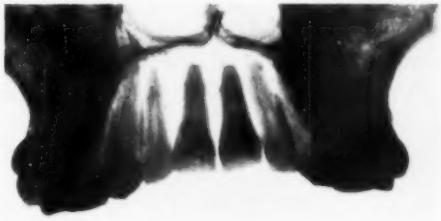


Fig. 11. Facies leprosa showing loss of the alveoli (cf. Fig. 10).

Fig. 10. Facies leprosa with atrophy and total loss of the alveoli leaving the teeth loose in the gingiva.

While the skeletal changes affecting the hands and feet thus do not differ in the mediaeval material from the changes described in contemporary lepers, cranial changes were found which — as far as is known — have not been described previously.

One of us (VILH. MOLLER-CHRISTENSEN) has, therefore, coined a new pathological term: »facies leprosa» which appears to be specific of leprosy. Facies leprosa is characterized by total atrophy of the anterior

nasal spine and disappearance of the external compact layers and also of the projecting parts of the facial bones on a level with the lower half of the nasal aperture of the skull. This gives the nasal aperture a peculiar appearance: Its breadth is increased, and the numerous exposed diploic cavities and vascular channels lend the bony surface the appearance of coarse pumice-stone, or as if it had been treated with coarse sand-paper (Fig. 9).

In addition, there is a characteristic atrophy of the alveoli of the four upper incisors spreading from the mid-line leading to exposure of the roots, so that in advanced cases these teeth are lost or become loose in the gingiva in vivo (Figs. 10 and 11). If the teeth are lost in vivo, an unmistakable »prolongation» of the corresponding lower incisors may be observed (Fig. 9).

Since these cranial changes have been found only in association with typical leprous changes of the hands and feet and have not been described in other diseases, it seems justified in assuming that »facies leprosa» is diagnostic of leprosy, particularly in the numerous cases in which skulls and calvaria are found detached from other bones.

To sum up, our studies of this material of skeletons have shown that the osseous changes in leprosy 400—700 years ago were identical with those occurring to-day. Moreover, our investigations have revealed previously unrecognized cranial changes which due to their characteristic appearance and easy demonstration (by roentgen) may prove of clinical significance in doubtful cases of leprosy.

SUMMARY

A study of 200 skeletons from a Danish mediaeval leper churchyard revealed in about half, leprous changes of the same character as those found in contemporary lepers. In addition, the writers describe specific leprous — hitherto unrecognized — cranial changes: »facies leprosa», characterized by disappearance of the anterior nasal spine and of the alveolar processes corresponding to the upper incisors.

ZUSAMMENFASSUNG

Das Studium von 200 Skeletten eines dänischen mittelalterlichen Leprafriedhofes zeigte in etwa der Hälfte der Fälle lepröse Veränderungen mit gleichem Charakter, wie man sie bei jetzigen Leprakranken findet. Darüber hinaus beschreiben die Verf. spezifische, bisher nicht beschriebene, lepröse Schädelveränderungen: »Facies leprosa», die durch das Verschwinden der Spina nasalis ant. und der Processus alveolares der oberen Vorderzähne charakterisiert ist.

RÉSUMÉ

L'étude de 200 squelettes, provenant d'un cimetière de lépreux danois du moyen âge, révéla dans à peu près la moitié des cas des altérations lépreuses du même type que celles constatées dans la lèpre contemporaine. En outre les auteurs décrivent des altérations crâniennes lépreuses spécifiques — inconnues à ce jour — le »facies lépreux» caractérisé par la disparition de l'épine nasale antérieure et du processus alvéolaire correspondant aux incisives supérieures.

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ROTATORY IRRADIATION

by

Howard Nielsen

When, in August 1941, rotatory irradiation was introduced at the Radium Centre, Aarhus, as a practical method of therapy, a number of difficulties with regard to dosage were at once encountered. For the purpose of creating a practical and useful basis for planning treatment a number of measurement experiments were made during the years that followed; the results of these experiments have been collected in a work which will now be summarized.

Whilst most of the authors who previously studied rotatory irradiation based their dosage on calculations or measurements in cylindrical phantoms, the experiments reported in this work comprised direct dose measurements in paraffin-phantoms, varying in shape (circumference) and structure (partly homogeneous, partly with embedded air cavities and bones), so that the phantoms corresponded to conditions in the human body. The chief aim of the work was an examination of the dose distribution to all regions of the body under varying conditions of irradiation: rotation angles from 90° to 360°, with change of the axis field, the centring and the quality of the rays. The dose distribution was represented graphically in about 125 isodose charts. Further, the work covered the measuring technique (for which purpose Sievert's condensor chambers were used), the determination of the absolute and integral doses, and from these an indication was given as to the most suitable irradiation scheme for a concrete task.

From examinations of the dose in cylindrical (homogeneous) phantoms the following conclusions may be drawn:

(1) *Surface dose* (Do/I) (*i. e.* surface dose (Do) in relation to free air dose (I) at target-axis-distance (50 cm)). Provided the height of the axis field remains constant, the surface dose is chiefly determined

Submitted for publication, Oct. 25, 1951.

by the illumination time, *i. e.* the width of the axis field, and is proportional to the latter (Figure 7 in the original paper). A change of the quality of the radiation in the range HVL 0.70—1.75 mm Cu is of no importance. The surface dose follows the inverse square law.

(2) *Axis dose* (Dx/I) (*i. e.* dose at the rotation axis (Dx) in relation to free air dose at target-axis-distance). This is measured in the rotation axis and, with changes of the physical factors, follows the same rules as the depth dose with fixed fields (Figures 11—12 in the original paper).

(3) *The percentage depth dose* (Dx/Do). With narrow axis fields this is considerable and it can be increased by means of hard radiation, long target-axis-distance and large rotation angle (360°).

(4) *The distribution of the radiation* is examined and is shown to change with the width of the axis field, the radius of the phantom, the quality of the rays, and the target-axis-distance. With fields not too wide, the distribution of the radiation is »bell-shaped» with the maximum dose around the rotation axis (if it coincides with the axis of the phantom, and the rotation angle is 360°) and with an even or a more abrupt decline towards the surface. Under certain conditions (wide fields) the maximum dose can be found to form a ring round the axis. Moreover, the representation of the three-dimensional dosage distribution in cylindrical phantoms is given (Figures 19—24 in the original paper), and its peculiarities are pointed out. The dosage distribution with rotation angles of 90° to 180° and 270° is illustrated by isodose charts (Figures 25—28 in the original paper).

From these fundamental experiments in cylindrical phantoms, the dosage distribution was examined in all the regions of the body which differ essentially from the homogeneous cylindrical phantom in circumference and content of bones and of air cavities. In this manner it was demonstrated that the body structure built up of media having different absorption factors for roentgen rays plays an important rôle in the dosage distribution and thus in the effectivity of the irradiation.

It is suggested that it is the most practical to fix the maximum dose in a cross-section of the body for irradiation at 100 per cent. and to express all other measured doses in relation to this. In the curves reproduced the conditions of irradiation are: target-axis-distance 50 cm, height of the axis field 15 cm, HVL 0.7 mm Cu. The width of the axis field and the rotation angle have been stated for each curve, as have also the quantity Dx/I. If the absolute dose at the rotation axis is known, expressed in per cent. of dose in free air (Dx/I × 100), it will be possible

to determine the absolute dose at every point in the cross-section by means of the isodose chart. It is shown quite simply by the isodoses that it will be possible to express the effect of the irradiation either in relation to the loading of the skin or in relation to the loading of other organs irradiated, which may perhaps in an individual case have lower tolerances than that of the skin.

In the *skull*, at a rotation of 360° and with centring over the pituitary fossa, isodoses are found which do not differ much from those in cylindrical phantoms (Figure 1). In semi-rotation over the side of the skull (Figure 2) asymmetrical isodoses are found. With the arrangement shown in

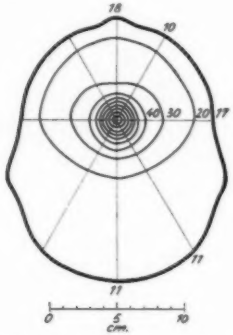

Fig. 1. Isodoses in the skull, centring in the pituitary fossa, rotation angle 360°, axis field 10 × 40 mm (Dx/I = 20.7 per cent.).

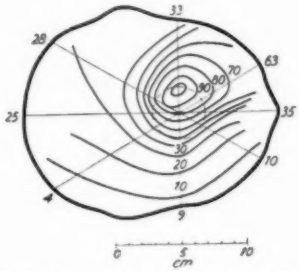

Fig. 2. Isodoses in the skull, centring in the pituitary fossa, rotation angle 180° over the side. Axis field 40 × 50 mm (Dx/I = 37.5 per cent.).

Figure 1 irradiation may, for instance, be given of a pituitary adenoma. The dose distribution is ideal: The narrow field (10 mm) gives a central core, measuring about 20 × 20 mm and outside which there is a very abrupt fall in the dosage. With a wider field of 40 mm the core will correspond to the axis field, and a uniform irradiation of this area is secured. The efficiency, reckoned as the ratio between the axis dose and the maximum skin dose, will be 550 per cent. and 270 per cent., respectively, in the two examples. If, for instance, a tumour dose of 3,000 r/20 days is desired, 750 r should be administered daily as a free air dose (Dx/I = 20 per cent.), the maximum loading of the skin being 540 r/20 days, localized to the nose and the temporal region.

In the *thorax* both the absolute dose and the dose distribution are changed appreciably by the cross-section, the content of air in the lungs and by the spinal bones, which could be shown experimentally with homogeneous phantoms and phantoms with embedded air-spaces and

bones (see Figures 33—55 in the original paper). If, for instance, it is intended to administer rotatory irradiation to an oesophageal carcinoma at the level of the bifurcation of the trachea, the radiation plan can be based upon the isodoses (Figures 3 and 4). With an axis field, measuring 5 cm in width, and a rotation angle of 360° the ideal dose distribution will thus be obtained with a dosage maximum surrounding the tumour as a cylinder. The skin is irradiated along a girdle-shaped area around the thorax, and the greatest loading will be anteriorly for a few centimetres on either side of the median line, whereas the dose on the sides of the thorax is much lower. The loading of the *lungs* near the oesophagus is comparatively

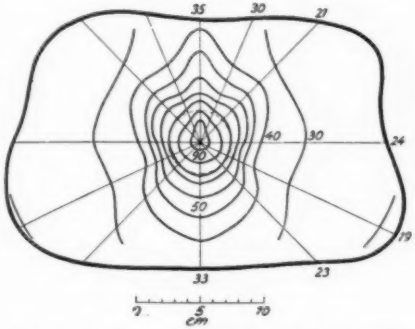

Fig. 3. Isodoses in the thorax, horizontal plane through the 7th thoracic vertebra, 360°, centring in the middle, width of axis field 5 cm (Dx/I = 56 per cent.)

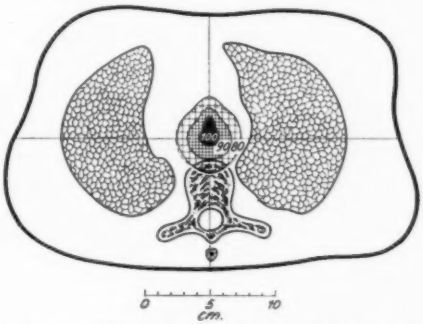

Fig. 4. Diagram of fig. 3, showing the extent of the central core in the cross-section.

slight; estimated in the middle of the lungs it will not be more than about 30 to 40 per cent. of the maximum dose. The *heart*, especially its posterior portions (the auricles), and the *trachea*, on the other hand, will be more or less involved in the central core. If the useful effect is stated as the ratio between the tumour dose and the maximum skin dose, it will in this case be 285 per cent. It is, of course, possible by means of the isodoses to state the *useful effect*, for instance in relation to the loading of the lungs or heart. If, for instance in a curative irradiation an attempt be made to obtain a tumour dose of 6,000 r/30 days, the daily dose in the tumour must be fixed at 200 r, which requires a free air dose (I) of 360 r daily (Dx/I = 56 per cent.). The maximum loading of the skin will then be about 2,100 r/30 days (corresponding to erythema of the skin). The dose in the pulmonary tissue will be as much as about 2,500 r/30 days, which should not involve any risk of its serious injury.

By means of rotatory irradiation with rotation angles of 90° to 180° (semirotation) it will also be possible to obtain an advantageous irradia-

tion of the osesophagus, but the useful effect becomes much less than in the case of complete rotation (see Figures 49—55 in the original paper).

The isodoses in the thorax show that all the theoretical advantages which can be expected from rotatory irradiation are obtained: the highest dose in the axis, an abrupt fall of the dose towards the surface. Add to this the fact that by means of transillumination during the irradiation the rotation axis can be centred in the tumour, and it will be readily understood that just in the treatment of oesophageal carcinoma, the first favourable clinical results have been obtained by means of this form of irradiation; this has been so even with a tumour so situated as to be considered intractable with cross-fire.

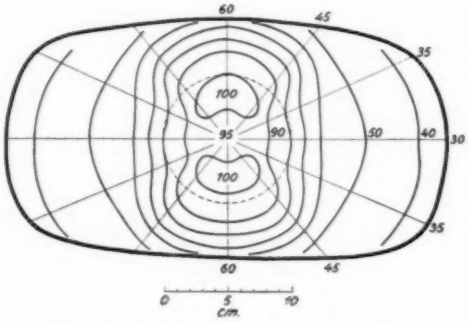

Fig. 5. Isodoses in homogeneous pelvic phantom, 360°, centring in the middle, width of axis field (dotted lines) 10 cm (Dx/I = 75.5 per cent.).

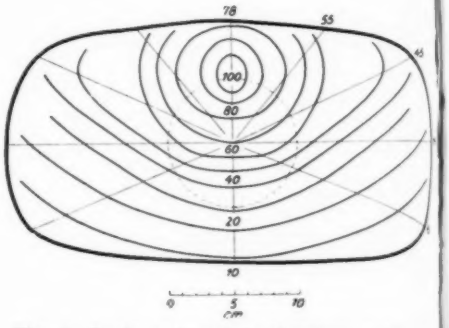

Fig. 6. Isodoses in pelvic phantom, rotation angle 180° over the anterior surface, centring in the middle, width of axis-field 10 cm (Dx/I = 69.5 per cent.).

The most interesting deviations from the dose distribution in cylindrical phantoms were found in the pelvic region. The experiments showed that the mere change from a cylindrical phantom to an oval phantom shaped like the pelvis changed the isodoses in a characteristic manner, and the presence of the pelvic bones accentuated these peculiarities in the course of the curves. With complete rotatory irradiation of a homogeneous pelvic phantom, isodoses are found which form sagittal ovals around the axis. With narrow fields one dose maximum is found in the axis, but with wider fields two maxima are formed in front of and behind the rotation axis (Figure 5). This splitting of the dose maximum becomes larger with a wider axis field and the maxima are withdrawn from each other (Figures 71—73 in the original paper). With a rotation of 180° over the transverse phantom diameter, the isodoses form ovals situated in front of the axis (*i. e.* between the target and the axis) with a dose maximum approaching the surface with increasing width of the

field (Figure 6). The dose decreases very rapidly behind the axis. Even if the axis is placed behind the centre of the phantom, the dose maximum cannot be made to penetrate more deeply under the surface by means of semirotation (see Figures 77—78 in the original paper). Semirotation over the side of the pelvic phantom (over the sagittal diameter) produces a dose maximum near the axis, but an abrupt fall occurs towards the side not irradiated; here, too, the dose maximum is split in the case of wide fields (see Figures 83—85 in the original paper).

The pelvic bones decisively change both the absolute dose and the course of the isodoses as compared to the isodoses in a homogeneous pelvis. Experiments with such a bone phantom showed that it was

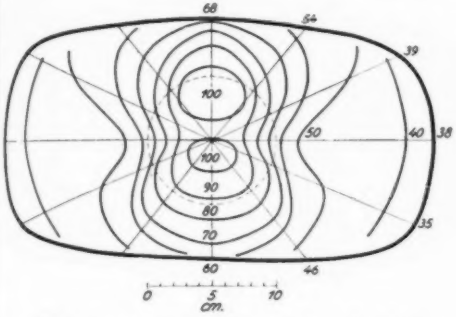

Fig. 7. Isodoses in pelvic phantom, plane I, 360°, centring in the middle, axis field 10 cm (Dx/I = 61.8 per cent.).

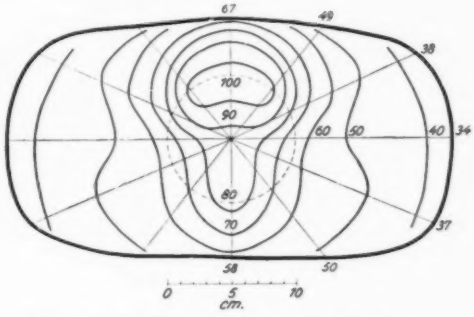

Fig. 8. Isodoses in pelvic phantom, plane III, 360°, centring in the middle, axis field 10 cm (Dx/I = 51.5 per cent.).

necessary to map out the dose distribution in at least 3 horizontal planes: one through the symphysis (plane I), one through the middle of the pelvis about 5 cm above plane I, and a plane through the promontory about 5 cm above plane II (plane III) (see Figure 70 in the original paper). Under the same conditions of irradiation widely different dose distributions were found in the three planes (Figures 7—8). (See also Figures 87—122 in the original paper.)

Summarizing it may be said: With complete rotation in plane I a central core is formed which in the case of small pelves and narrow axis fields is situated in front of the centre of the pelvis, whilst in large pelves it forms an elongated oval along the sagittal diameter. With wider axis fields the dose maximum is split, and in certain cases also in the central core, so that only about 75 per cent. of the maximum will be obtained in the rotation axis (Figure 107 in the original paper).

In planes II and III the isodoses are changed so that only one dose maximum is formed (both in small and large pelves), situated in front

of the centre, and so that the dose maximum is forced more anteriorly with increasing width of the axis field. Semirotation over the anterior surface of the pelvis produces the same isodoses as in a homogeneous phantom, whilst rotation over the posterior surface results in different curves (in plane III) because of the large massif of bones.

Semirotation over the side of the pelvis produces a thorough splitting of the dose maximum — which will be situated quite outside the pelvic bones — immediately beneath the surface of the skin, whilst a dose of about 70 per cent. only is obtained in the axis (see Figures 109—111 in the original paper).

The isodoses have been constructed in such a manner that they may be added, and thus it becomes possible to obtain a general view of the dose distribution in combined rotatory irradiations — provided the rotation axes are the same in the irradiations.

The practical tasks which may be met with in deep irradiation of the pelvis may be summarized in the main as follows: (1) Homogeneous irradiation of the entire pelvis minor, (2) selective irradiation of the uterus (or the prostate), (3) irradiation of the uterus and the parametria, (4) irradiation of the urinary bladder, and (5) irradiation of the rectum and the sigmoid flexure.

From the isodoses covering the pelvis it was possible to decide whether the tasks mentioned above could be performed effectively by means of simple or combined rotatory irradiation. Further, a general idea could be obtained of the dose distribution and the absolute dose in combined radium-roentgen irradiation in cases where the isodoses were known for the radium aggregate employed.

Though it might have been expected that the pelvis minor could have been covered by a homogeneous irradiation applied merely by rotatory means, the isodoses applying to the pelvis showed that this was by no means the case. Even with wide axis fields, covering or even exceeding the borders of the pelvis, two dose maxima were formed anteriorly and posteriorly (*i. e.* corresponding to the rectum and the bladder), whilst a triangular area, lying laterally in the transverse diameter (*i. e.* corresponding to the parametrium), received doses of less than 80 per cent. of the dose maximum (Figure 9). Thus a homogeneous irradiation of the pelvis minor is not

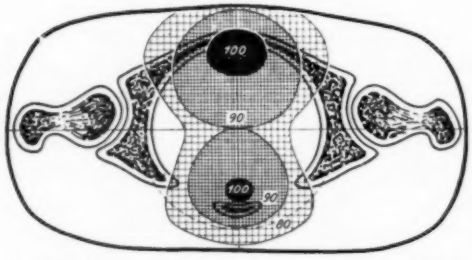

Fig. 9. Diagram showing extent of central core in pelvic phantom, plane I, 360°, centring in the middle, axis field 15 cm (Dx/I = 74.4 per cent.).

possible by means of simple or combined rotatory irradiation (see Figures in the original paper).

Selective irradiation of the uterus and its immediate surroundings can only be effected by means of contact roentgen or radium. It is possible by means of rotatory irradiation to cover the cervix and corpus uteri with a dose maximum equal to, or twice, the maximum skin dose, but only with a simultaneous intense loading of the adjacent organs (the rectum and the bladder).

It might be expected that the tasks mentioned in (4) and (5) could be solved by means of semirotation over the anterior and the posterior surface of the pelvis, respectively, however, closer examination shows that irradiation of the deepest parts of the urinary bladder (the trigonum and the fundus vesicae, *i. e.* more than about 7 cm beneath the surface) can be best effected by means of a combined technique. Thus rotatory irradiation (360°) with an axis field of 5 cm plus an additional irradiation at 90° rotation over each side of the pelvis (Figure 11) will give the best dose distribution: A high tumour dose with the lowest dose on the skin and in the rectum (for instance, tumour dose 6,000 r, skin dose 3,700 r and dose in the rectum 3,000 r). An excellent irradiation of the more superficial parts of the bladder (the corpus vesicae) is obtained by means of semirotation over the anterior surface (Figure 6); the rectum can thus be spared entirely, but the *useful effect* is only about 130 per cent. With regard to irradiation of the rectum and the sigmoid flexure, it can be deduced from the curves that 360° rotation is to be preferred in the case of very large tumours of the rectum, as they will best be covered by this means, but otherwise semirotation over the posterior surface should be used. In all these forms of irradiation a *useful effect* of about 130 per cent. is obtained; thus, it is the tolerance of the skin that decides how high the tumour dose may become.

In the case of irradiation of cancer colli uteri an attempt will be made to irradiate the uterus and the parametria with a large dose and at the same time to restrict as much as possible the irradiation of the rectum and the bladder — provided these organs are not involved in the process. The irradiation plan must, of

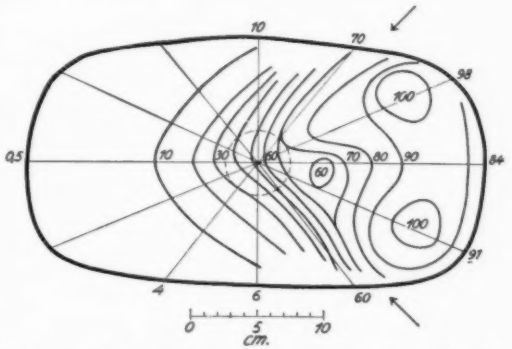

Fig. 10. Isodoses in pelvic phantom, plane I, rotation angle 90° over the side, centring in the middle, axis field 5 cm (Dx/I = 25.6 per cent.).

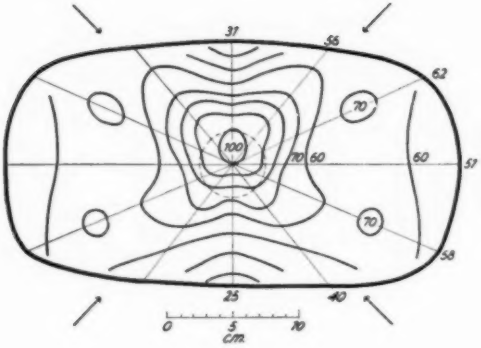

Fig. 11.

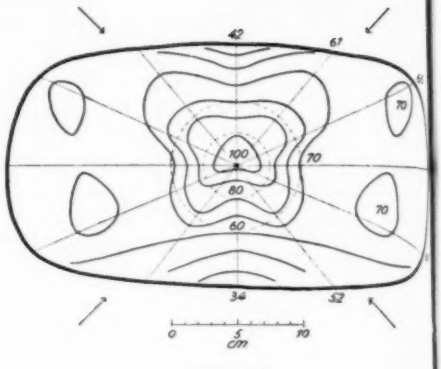

Fig. 12.

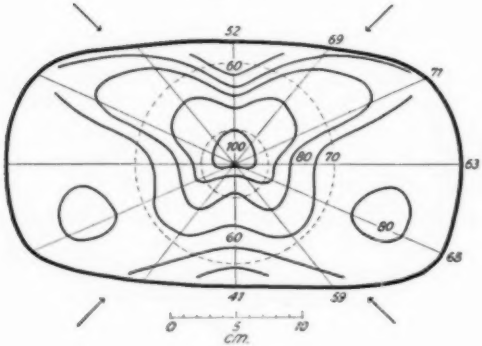

Fig. 13.

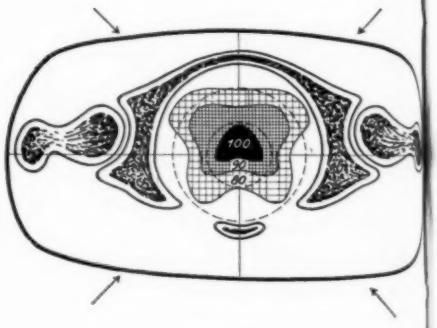

Fig. 14.

Fig. 11—14. Isodoses in pelvic phantom, plane I, combined rotatory irradiations: (a) 90° from either side (as fig. 10) and (b) 360°, axis field 5 cm (fig. 11) (Dx/I = 31.4 per cent.), 360°, axis field 10 cm (fig. 12) (Dx/I = 37.7 per cent.), 360°, axis field 15 cm (fig. 13) (Dx/I = 41.8 per cent.). Fig. 14 is a diagram of conditions in fig. 12.

course, be made in the individual case after the extent of the tumour in all dimensions has been thoroughly mapped out.

As shown by the isodoses, effective irradiation confined to the uterus and the parametria cannot be obtained by simple rotatory means. A combination of 360° rotation, centred in the middle of the pelvis and with axis fields of 5, 10 and 15 cm, respectively, and 90° rotation over the side of the pelvis with an axis field of 5 cm (Figure 10) resulted in dose distributions as shown in Figures 11—14. In contrast with simple rotatory irradiation these combinations produce *an aggregate* dose maximum

situated around and chiefly in front of the centre, with comparatively slight loading of the rectum (reckoned 5 cm behind the centre). Strangely enough it was not found possible to move the limits of the central core much more laterally in the parametrium, as the 80 per cent. isodose for the three examples intersects the transverse line 3.2, 4.0 and 4.2 cm respectively from the centre. The combination shown in Figures 12 and 14 seems to be the best, with a useful effect of 155 per cent., a core covering the uterus, the posterior part of the bladder and about 4 cm of the parametrium on either side of the centre, whereas the rectum is relatively spared: receiving about 60 per cent. of the dose maximum. It is, of course, possible to vary the combined irradiations in numerous other ways besides those described here, and the advantages which may be obtained by means of a combination of rotatory irradiation with fixed fields or radium have also been calculated. An example of the doses and the dose distribution which may be obtained by combining rotation and a radium aggregate with known isodoses has been given in the paper (Table 8 in the original paper).

A factor to which increasing attention has been paid during recent years is the concept of the *integral dose*, which is of essential importance to the patient's general health in massive irradiations. It was shown in the paper how it is possible to calculate from the isodoses the *total* integral dose for a given rotatory irradiation, or the *relative* integral dose, as the ratio between the dose in the tumour and the total dose. However, it will presumably be safer and easier to undertake direct measurements of the integral dose by an arrangement as suggested by GRIMMET.

As is known, both the surface dose and the depth dose in fixed-field irradiations change with the size of the field, the target-skin-distance, the quality of the irradiation and the thickness of the layer of tissue; by means of tables it is thus easy to determine the dose everywhere in the region in the case of cross-fire. It is true that none of these dose tables have been corrected for the change of dose produced by the presence of air and bones in the regions, as the tables were based upon experiments with phantoms. In conformity with the rules applying to fixed fields, the absolute dose in the case of rotatory irradiation changes with the conditions of radiation. As the target-skin-distance constantly changes in the course of the irradiation, it is most practical to base the calculation of the dose on the axis dose (Dx), which is measured at a constant distance from the target. As shown previously, all doses in the cross-section can be calculated with this initial value from the isodoses applying to the irradiation in question.

The phantom experiments showed that the axis dose (Dx) changed in a regular manner with the size of the axis field (A. cm^2), so that the formula: $\log Dx = \log A + b$, applies to axis fields between 75 and 225

cm^2. When one value of the axis dose in the cross-section is thus known, the axis dose can be calculated for all field sizes.

Further, it could be shown that the axis dose was dependent of the cross-section of the body, so that the sagittal (a) and the transverse diameter (b) determined the size of the axis dose. The formula arrived at empirically: $Dx = 163.7 - 3.1\ a - b$, is sufficiently accurate to be used under practical conditions.

Two factors of decisive importance to the size of the axis dose are the content of air (in the thorax) and of osseous tissue (the pelvis) in the body. It was rather surprising to find that the axis-dose is practically the same everywhere in the thorax, whether it was measured at the level of the 1st or 10th thoracic vertebra. A correction of the axis dose for the individual amount of air cannot be effected; it would be necessary to undertake direct measurements, for instance by introducing a small chamber into the oesophagus during irradiation. It is difficult to decide how much individual changes in the density of the bones will influence the axis dose in the pelvic region, but variations in the external measurements, *i. e.* the diameters a and b, may be corrected by means of the formula mentioned above.

It goes without saying that in order to work with rotatory irradiation on an equal footing with current cross-fire irradiation, it is necessary to have the same general view of the absolute dose and the dose distribution as in the latter technique; only then can rotatory irradiation be included in the actinotherapeutical instrumentarium as an excellent technique of irradiation in selected cases. Rotatory irradiation should not be used uncritically for any task, but should be planned just as carefully as other deep therapy.

SUMMARY

The paper is a summary of the main points in the author's publication of 1948, which deals with the dose problems in rotatory irradiation.

ZUSAMMENFASSUNG

Der Bericht enthält eine Zusammenfassung der wichtigsten Punkte einer Publikation des Verf. aus dem Jahre 1948 über Dosisprobleme bei der Rotationsbestrahlung.

RÉSUMÉ

L'article représente un résumé des points essentiels contenus dans la publication faite par l'auteur en 1948 sur les problèmes du dosage dans la cyclothérapie.

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FROM THE RADIUM CENTRE (DIRECTOR: JENS NIELSEN), COPENHAGEN, DENMARK

THE ORGANIZATION OF RADIOTHERAPY

by

Jens Nielsen

The duality which is a physical characteristic of ionizing, penetrating rays is manifest also in another sphere: in their medical application.

From the very outset, it was evident that radiology would embrace two widely different and clearly defined medical fields: diagnosis and therapy. The development has been along peculiar and unpredictable lines. Diagnosis, which in a way would seem easier and simpler, aiming only at scientific examination without any suggestion of active influence, soon overcame its inherent tendency to dispersion as a sub-speciality of many other specialities and has everywhere attained the status of a recognized independent speciality. On the other hand, therapy — apparently predestined for rapid development as an autonomous entity — still remains in a transitional stage of incomplete development and organization.

It is not difficult to elucidate the cause; it is both historical and essential.

In retrospective, it seems but natural that the pioneers of radiology had to explore the diagnostic and therapeutic possibilities concurrently. It cannot cause surprise that the apparently obvious and natural connection between these two main branches — a connection which at first glance would seem to be due to physically and technically fundamental, elementary relationships, but which upon closer consideration is found to be due merely to their initial character — has been an important factor in development during the first half century; it is evident to this day.

In the course of time, however, it was inevitable that the fundamental differences between the two new medical spheres, auxiliary diagnosis and clinical radiotherapy, should grow ever more marked.

Read before the 17th Congress of the Northern Association for Medical Radiology, Aarhus, June 13, 1951; submitted for publication November 11, 1951.

The fact that complete separation has not yet taken place is due int. al. to the early association of radiotherapy with the treatment of cancer. The foresight, unique enthusiasm, and administrative talent of eminent personalities, such as FORSSELL and REGAUD, gave rise to the extremely fruitful association of the fight against cancer with radiotherapy, to the benefit of both.

In this connection, radiotherapy has not only contributed to the organization and centralization of cancer therapy on a broad base as well as to the permanent character of the results, but it has also afforded entirely new impulses for cancer research. In return for the big and still unfulfilled promises which radiotherapy gave to cancer problems, radiotherapeutic centres have afforded a chance — which would otherwise have had to be awaited until our day — for research within the fundamental branches of medical radiophysics and radiobiology. At the same time, radiotherapy ran the risk of losing itself by over-specializing and isolating itself in the numerous obscure problems of a causal, formal and functional nature presented by cancer and of neglecting its inherent possibilities as a fundamental therapeutic entity.

This gave rise to a special experimental form of cancer therapy, mainly with radium and to apparently more simple, accessible radiotherapy of benign lesions. While the former has become ever more intricate and difficult, requiring ever growing auxiliary apparatus, the latter has tended to be decentralized and combined with roentgen diagnostic work.

The result may be seen to-day in Denmark and several other countries: a few purely radiotherapeutic clinics, or rather institutions of complicated structure, existing primarily for the treatment of cancer, and a large number of mixed diagnostic and therapeutic hospital departments acting as regular, indispensable links in modern hospital organization. In the latter departments, diagnosis is the main occupation,while radiotherapy is subordinate and concerned essentially with benign lesions, although it is used also for the palliative or adjunctive treatment of malignant disease. The fortuitous nature of this division will be seen int. al. from the fact that to this very day radiotherapy in breast cancer has been reduced, to a large extent, to a standardized pre- or postoperative form of roentgen treatment which may be performed in any clinic; on the other hand, the far more simple treatment of skin carcinoma is strictly centralized.

Owing to FORSSELL's foresight, the Scandinavian countries outside Sweden have been spared — though not with the completeness and ease of the mother country — the radiosurgeons who existed in the Germanic, Roman, and Anglo-Saxon countries until it was realized that a combination of surgery and radiotherapy in the same person may prove unfortunate. The large university hospitals are now creating their own purely

diagnostic departments. The same applies to a few specialized hospitals (tuberculosis, neurosurgical etc.). For historical and other reasons, Sweden has for a long time had a special branch of therapy: radiogynæcology. — Time draws a distinct pattern for future development: roentgen diagnosis and therapy as two large fundamental branches on the broadest basis; and these must be expected to subdivide gradually into groups covering particular organs, regions, and diseases.

At this stage, when roentgen diagnosis in Scandinavia may be said to be well-established and consolidated, although still rapidly developing and radiotherapy is at last being recognized as an independent therapeutic basic discipline, a new and revolutionary event is disturbing the picture. This novelty also arises in the realm of physics, this time: nuclear physics —artificial radioactivity. We witness an entirely different and much more rapid development. Radioisotopes — a sort of by-product in nuclear reactions which are predominantly of political and military significance on a world-wide scale — have not merely opened the door to internal radiotherapy, but are creating a new form of radiodiagnosis on the atomic plane by the indicator method; this invokes the aid of medicine as well as physiology and biology in the widest possible sense. They have imparted a particularly strong impetus to radiobiology. Their practical and fundamental significance and scope are clear. Where previously only a few, scattered efforts were at work, the enormous afflux is now bursting all bounds. The establishment of an international organization of radiobiology gives some idea of what is happening.

It is difficult to foretell the reaction of classical, conventional radiotherapy in its present state of incomplete organization. Ultimately, it is bound to benefit by this extension of its scope, but it is not unlikely that it will undergo another temporary weakening and diaspora by reason of its weak organization and involvement in cancer therapy.

If we are right in believing that radiotherapy is essentially a fundamental medical therapeutic entity, it will of course be re-established and, due to its inherent value, persist and undergo further development. Nevertheless, development may be delayed, distorted and may have to go through periods of sterility.

In this situation, when a new generation is coming forth, faced not only with the adaptation of old tasks, but also with the solution of new problems and future planning, I think that we radiologists should be observant, alert, and in contact with progress. If we consider that we have accumulated valuable knowledge and experience, it is our duty to utilize it and introduce it in a sensible manner into the dynamic evolution which we must give a fruitful course as far as is within our power. Our voices must be heard and they must have weight. We cannot demand or expect outsiders to understand our wishes and accomplish our aims. And we must

start in our own circle, with the radiologists. In my opinion, we must build our organization and plans on the dichotomy inherent in radiotherapy. This calls for individual resignation and concentration. But time is relentless in ever-increasing specialization, and in the long run each individual is happier if his life's work lies in, rather than against development. After all, will anyone now maintain that the combination of roentgen diagnosis and radiotherapy is successful and fruitful, or deny that in effect it exists only from tradition? The two main branches of the stem of radiology are growing farther and farther apart, giving off new branches, twigs, leaves, and flowers. At the same time the hitherto tender, but early shoots from the main stem, radiophysics and radiobiology, are now flourishing and growing like the beanstalk in the fairy tale.

By recognizing and admitting the fact that radiotherapy and roentgen diagnosis follow separate paths and advocating the organization of medical radiology in two basic fields — diagnosis and treatment — we may perhaps err in some, but not in important respects.

We may recapitulate and consider how far we have progressed in development as far as radiotherapy is concerned. By virtue of FORSSELL and his collaborators, contemporaries, and successors: BERVEN, HEYMAN, SIEVERT and REUTERWALL, Sweden has become of course a model for the other Scandinavian countries. Even so, radiotherapy is — or is being — recognized as a medical speciality and has been introduced as an independent subject at all medical schools in Scandinavia. The radiotherapeutic institutions for cancer treatment and research are becoming recognized university clinics, but only Sweden has as yet established the less complicated, and less expensive regular therapeutic hospital departments. To avoid stagnation, they are indubitably necessary and they have proved their right to exist and their functional capacity in Great Britain. There, the organization may seem to the outsider based perhaps too much on radiophysical and technical aspects which have therefore formed a strong foundation and superstructure; at any rate, it is firmly established and effective. The method of organization emphasizes that radiophysics is an indispensable support of radiotherapy; it demonstrates that satisfactory radiotherapeutic departments of smaller size and less complicated structure than what become gigantic cancer therapeutic centres may be established; and further that these may function mainly on this principle which apparently is the most simple and most easily practicable one. The system is now followed in U. S. A., where, up to now, radiotherapy cannot be said to have gone through a happy development period, as well as in subcontinents like India which is practically virgin soil in this respect.

Compared to surgery, which has already been subdivided into specialities associated with particular organs, regions, and diseases, it must be

admitted that radiotherapy is more difficult and more dangerous, not only because its action is less direct and less immediate, but because it requires larger and more complicated apparatus. And yet, it is presumably in a far more primitive, undeveloped technical stage, resting upon a deficiently elucidated theoretical basis, yet demanding thorough clinical experience.

Some might perhaps believe that comparison with a smaller therapeutic subject, such as physical therapy, would be more fitting. On further consideration, however, I feel that most of these objectors would realize that such comparison is not possible and that in fact radiotherapy is a fundamental therapeutic subject of an original nature, a separate entity.

Let the point be stated quite frankly: One of the first administrative questions to be asked, preferably not by outsiders, but by ourselves, is without a doubt: Does simple, light radiotherapy and minor radiotherapy, still belong to roentgen diagnosis or ought it to be taken over by special radiotherapeutic departments? To some of us, this question may seem difficult to answer, but it is urgent, particularly when considering the large hospitals of more than 1,000 beds.

I write as an adherent of and advocate for the division of radiology into diagnosis and therapy and plead for its execution. I believe it to be both inevitable and useful.

One of the first steps to be taken along this road would be the establishment of a Section for Medical Radiotherapy as a Sub-section of the Northern Association for Medical Radiology. Sweden can take this step on her own to-day, but in the other Scandinavian countries development is too far behind and the pure radiotherapists too few to form therapeutic sections for each country. Therefore, it would further the development, if the Scandinavian section were to be established before those of the individual countries.

Whether the scope of such a radiotherapeutic society ought to be narrow or wide is less essential than its establishment. To-day international congresses are formally, and the Scandinavian congresses actually, divided into roentgen-diagnostic, radiotherapeutic, radiobiologic and radiophysic sections.

Radiotherapy must remain of course in the mother-house of radiology. By recognizing the plurality of radiology, we are not attacking its integrity, but supporting it.

SUMMARY

The author submits some personal reflections on the evolution of radiotherapy.

ZUSAMMENFASSUNG

Der Verfasser legt einige persönliche Betrachtungen über die weitere Entwicklung der Radiotherapie dar.

RÉSUMÉ

L'auteur soumet quelques réflexions personnelles sur l'évolution de la radiothérapie.

FROM THE RADIUM CENTRE FOR JUTLAND (DIRECTOR: PROFESSOR CARL KREBS), AARHUS, DENMARK

CARCINOMA OF THE CERVIX FOLLOWING SUPRACERVICAL HYSTERECTOMY

by

Kai Nielsen

Cancer arising in the cervical stump is not extremely rare. Thus, more than 1,000 cases have been reported in the German literature alone (3). As is well-known, all these reports have given rise to heated discussion as to whether, for prophylactic reasons, supravaginal hysterectomy should not be replaced in all cases by the more extensive total hysterectomy.

TRUELSEN (6), in his thesis on cancer of the uterine cervix, discussed the problem in detail. In a comprehensive series consisting of nearly 3,000 cases from the Radium Centre, Copenhagen, there were only 28 cases of cervical stump cancer, *i. e.* less than 1 per cent, showing that the condition is not common, even in a large radiotherapy department.

In a ten-year material from the Radium Centre, Aarhus, comprising the years 1937—46 there were 16 cases of cervical stump cancer among 1,219 cases of cancer of the cervix uteri, *i. e.* 1.31 per cent.

Two different types must be distinguished: (1) true stump cancers in which the malignant tumor actually develops in the residual cervical stump sooner or later after the corpus uteri has been removed, and (2) coincidental cases in which cancer was either actually, or in all probability, present at the time of operation.

In the series presented here *12 unquestionable true cancers* were found. The age of these patients ranged from 45 to 73 years and averaged 55.2 years. Intervals ranging from 6 to 35 years and averaging 19.2 years had elapsed from the supracervical hysterectomy to the recognition of the stump cancer.

In 4 cases, the indication for the supracervical hysterectomy had been inflammatory adnexal disease and bilateral salpingo-oophorectomy

Submitted for publication, Oct. 30, 1951.

was performed in addition to amputation of the uterus. In the remaining 8 cases, the indication for operation had been fibromyoma uteri; in seven of these in which it was possible to procure information, one or both ovaries were left intact.

It has been discussed whether the preservation of ovarian function has an accelerating or inhibiting influence on the development of a carcinoma of the cervical stump. Most investigators claim that cancer develops more rapidly when ovarian function is preserved than when it is abolished, while a few writers maintain that the sudden involution of the genital organs, including the cervical stump, following bilateral salpingo-oophorectomy leads to changes favoring the development of cancer.

The present limited series seems to lend support to the former view, since the interval between the operation and the recognition of the stump cancer in the 4 cases in which bilateral oophorectomy had been performed, ranged from 20 to 33 years and averaged 25 years, whereas it ranged only from 6 to 20 years and averaged 14.1 years in the 7 cases with preserved ovarian function.

Two of the 12 patients, and presumably a third, had never been pregnant.

The symptoms were those usually encountered in cancer of the cervix.

Bleeding was present in all 12 cases, while contact bleeding was found only in two of these elderly women. Vaginal discharge was observed in five, pain in four and general symptoms, fatigue and loss of weight in three cases. None of the patients presented vesical or rectal symptoms.

The initial symptom was bleeding in nine cases, vaginal discharge in two, and pain and discharge in one case. It would be expected that these women who had not menstruated for years would be particularly aware of the significance of the appearance of gynecological symptoms, notably bleeding, and this actually seems to have been the case. Of these 12 patients, eight applied for medical aid within the first fortnight after the onset of symptoms, two waited 3—4 months, one 10 months; only one did not consult her doctor until after the lapse of two years because, as she put it, »the bleeding could not come from the uterus».

The doctors also seem to have been aware of the serious nature of the symptoms, since only one patient (with comparatively slight symptoms) was not referred to hospital until after the lapse of five years. On admission her cancer was in stage II but she is still living and well 9 years after radium and roentgen treatment. The remaining 11 patients were referred for hospital or specialist examination at once or at least within the first month. After having been examined by a specialist, two of these patients were treated with irrigations for six months and two years,

respectively, before the proper diagnosis was secured by biopsy. At that time their cancers were in stage III and I, respectively, but they survive symptom-free with observation periods of 8 and 6 years.

On admission to the Radium Centre, four patients were in each of the stages I, II, and III, but none in stage IV.

Histological examination revealed adenocarcinoma in one case and squamous-cell carcinoma in eleven. The patients were given ordinary radium and roentgen treatment with the difference that, owing to the absence of the uterine cavity, a short tube was used only in one case.

Seven of the 12 patients (*i. e.* nearly 60 per cent) are alive and symptom-free after an observation period of from $5^1/_2$ to 11 years, while the others have died of or with the growth; in one of the latter no information is available as to the cause of death or a possible recurrence of the cancer within the five-year period.

Complications of treatment were inconspicuous; there were no rectal or vesical fistulae.

Coincidental Cases

These 4 cases were diagnosed at latest 15 months after the operation.

Case 1. The patient (501/1938), aged 46, had undergone unilateral oophorectomy in 1912. She had menstruated regularly since but had never been pregnant. Fifteen months prior to admission to the Radium Centre she entered another hospital for menorrhagia which had persisted for three weeks. A fibroma of the uterus was disclosed, and supravaginal amputation with removal of the fibroma, the size of a child's head, was performed. After that time she felt well until a fortnight before admission when profuse bleeding developed. She was at once admitted to the Surgical Department where a fairly large, predominantly endocervical, growth was revealed; a small, slightly elevated, vulnerable tumorous mass was situated on the anterior cervical lip. The cervical stump was freely movable; no lateral infiltration, *i. e.* stage I.

A diagnostic excision showed squamous-cell carcinoma. She was transferred to the Radium Centre and given radium in two sittings, each of 2,880 milligramme-hours and roentgen treatment, 4,800 r. She survives symptom-free with an observation period of 10 years.

Several authors (1, 2, 4), in their reports on series of cervical stump cancer with considerable numbers of coincidental cases, emphasize the importance of a thorough gynecological examination prior to any supravaginal amputation, and notably of the employment of cervical dilatation and curettage in all cases where inspection of the portio does not arouse suspicions justifying a biopsy (2).

It is likely that it would also have been possible to demonstrate cancer 15 months previously by these measures in the case reported above. The considerable bleeding alone which occurs after the dilatation of an endocervical tumor, even in the incipient stage, might have aroused suspicion.

In the second case reported below there is not the least doubt that such measures would have secured the diagnosis, so that supravaginal hysterectomy would have been avoided.

Case 2. The patient (2236/1942), aged 50, mother of two children, began to bleed again two years after she had passed the menopause. The bleedings were very variable in intensity, duration and interval. After the lapse of three months, pain in the left iliac fossa developed simultaneously with the bleeding, for which reason she applied for medical aid and was at once admitted to the local hospital; enlargement of the uterus was disclosed and supravaginal amputation performed. A mandarin-sized fibroma was removed; the cervix was found to be friable, but total hysterectomy could not be accomplished on account of the general condition of the patient. Histological examination of the specimen removed at operation showed a simple fibromyoma together with a solid carcinoma of the cervix uteri, for which reason she was transferred to the Radium Centre three weeks after operation. The portio was found to be somewhat flattened, slightly broader than normal, slightly irregular, with small prominent nodules and overgrowth into the vaginal vault partially obliterating the fornices. On vaginal examination tumor masses of considerable extent were palpable lying anteriorly close to the bladder and towards the right pelvic wall, where a walnut-sized node was felt. Thus, the condition was predominantly one of a endocervical cancer in stage III, which must be supposed to have been, at first, entirely endocervical. After combined radium ($2 \times 1{,}920$ milligramme-hours) and roentgen treatment (9,400 r) the patient was fairly well for more than one year, but was then re-admitted with radiating pain and the pelvis filled with tumor masses; urography showed absence of excretion on the left side. She was given palliative treatment but succumbed in the course of another year, with a rectovaginal fistula in the terminal stage.

The case plainly illustrates the well-known fact that caution should be exercised in allowing a fibroma to be labelled as the cause of persistent postmenopausal bleeding.

Case 3. The patient (1843/1944), aged 41, had had 5 pregnancies terminating normally. In the intervals she had menstruated regularly and never presented any gynecological abnormalities. Her sixth pregnancy had also shown a normal course without vaginal bleedings, but during the parturition she was referred to the local hospital on account of protracted labor and cessation of fetal heart sounds. The uterine contractions were very painful until shortly before admission when they changed in character and suddenly, practically ceased. In hospital she was delivered by forceps of a full-term dead baby weighing 4,000 g. Manual removal of the placenta was carried out 15 minutes later. It was then disclosed that rupture both of the bladder and the uterus had occurred. Laparotomy was at once performed; blood and fluid in the peritoneum and a large rupture of the left parametrium and of the lower part of the anterior surface of the uterus were found, for which reason supravaginal amputation of the uterus and bilateral salpingo-oophorectomy were done. Apart from the development of a vesicovaginal fistula, the postoperative course was uneventful, and the patient was discharged 6 weeks later. For the next six months she lived at home without any discomfort, apart from constant leakage of urine through the fistula; there was no suggestion of vaginal bleeding.

After that time lumbar pain developed, particularly on the right side; it was accompanied by a moderate elevation of the temperature to about 38° (maximum 39°), and she was readmitted to the local hospital, where a urinalysis revealed the presence of numerous leukocytes. S. R. 83 mm/hour; Hb. 87 per cent. A vaginal examination dis-

closed a partly necrotic ulcer crater in the vaginal vault, surrounded by large hard tumor masses extending from one pelvic wall to the other, encircling the rectum and extending well downwards in the rectovaginal septum. No actual opening of the fistula into the bladder could be found, but there was constant leakage of urine and undoubtedly extension of the growth into the bladder. A diagnostic excision showed carcinoma (stage IV).

The patient was transferred to the Radium Centre and received intense radium (2 × 2,580 milligramme-hours) and roentgen treatment (5,400 r given by rotation technique), but died 4 months later.

It can scarcely be doubted that the cervical cancer had been present at the last parturition and that it was responsible for the rupture although readily understandable that it passed unrecognized. The forceps delivery might have been responsible for the rupture, and the condition of the tissues in a combined rupture of the bladder and uterus might easily disguise any abnormality at laparotomy. Furthermore, as there was not the slightest indication of vaginal bleeding, and the vesicovaginal fistula and pyuria lent support to a diagnosis of pyelitis (the pain was actually referred from the pelvic tumor infiltrations) it may welbe understood how the condition in its later course also escaped recognil tion.

Case 4. The patient (1091/1946), aged 38, had undergone supravaginal amputation for a fibromyoma seven months before her admission to the Radium Centre. Two months after the operation she had contact bleeding. Within the next month she sought medical advice and was at once referred to the nearest central hospital where a suspect erosion was disclosed. Repeated diagnostic excisions resulted in an increasing suspicion of cancer. She was then transferred to the Radium Centre, where she received radium treatment (two sittings each of 1,920 milligramme-hours) but no roentgen therapy. She is now alive and well after an observation period of 5 years.

The Problem of Supracervical or Total Hysterectomy

One of the difficulties encountered in deciding the incidence of true cervical stump carcinoma is due to the failure to follow up a sufficiently large number of cases of supravaginal hysterectomy over sufficiently long periods. However, the consistent centralization of the treatment of cancer in a well-defined district may make it possible to obtain a rough estimate by comparing the number of stump cancers treated in a radiation therapy institution with the number of supravaginal hysterectomies performed in the district in question.

From the annual reports from the hospitals in Jutland it was ascertained that in the year 1941 at least 250 supravaginal hysterectomies were performed in the district served by the Radium Centre for Jutland at Aarhus.

In view of the greater centralization and the increased surgical activity which have taken place during the years and the uncertainty to which such a rough estimate is subject, the number of supravaginal

hysterectomies in a ten-year period may be fixed at 2,000 or even 1,000 instead of 2,500. It will then be seen that the 12 cases of true stump cancer in this ten-year material give an incidence of the order of magnitude of 1 per cent — scarcely justifying the abandonment, for prophylactic reasons, of the supracervical operation in suitable cases. As pointed out by TRUELSEN, the fact that the prognosis of true stump cancer is not at all unfavourable lends further support to this view.

SUMMARY

In 16 cases of cervical stump cancer in a 10-year material comprising 1,219 cases of cancer of the uterine cervix, 12 cases of true stump carcinoma and 4 coincidental cases were found. The latter are reported in detail. The incidence of true cervical stump carcinoma is estimated at not more than about 1 per cent, which, the author feels, hardly justifies the abandonment of the supravaginal operation, particularly in view of the fairly favorable prognosis of true stump cancer.

ZUSAMMENFASSUNG

Unter 16 Fällen von zervikalem Stumpfkrebs in einem 10 Jahre umfassenden Material von 1.219 Fällen von Cancer cervicis uteri fand man 12 Fälle mit wirklichem Stumpfkrebs und 4 damit übereinstimmende Fälle. Die letzteren werden in allen Einzelheiten wiedergegeben. Die Häufigkeit von wirklichem zervikalen Stumpfkarzinom beträgt schätzungsweise nicht mehr als 1 Prozent; dieses rechtfertigt nach Ansicht des Verf. kaum das Verlassen der supravaginalen Operation, besonders wenn man die ziemlich günstige Prognose des wirklichen Stumpfkarzinomes beachtet.

RÉSUMÉ

Sur 1,219 cancers du col utérin, réunis en 10 ans, 16 étaient des cancers du col restant, comprenant 12 cas de véritable cancer du moignon et 4 cas de cancer concomitant. Ceux-ci sont décrits en détail. La fréquence du véritable cancer du col restant est estimée à 1 % au plus, ce qui, selon l'auteur, ne justifie guère l'abandon de l'hystérectomie subtotale, surtout si l'on tient compte du pronostic assez favorable du vrai cancer du col restant.

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR: JENS MUNCK NORDENTOFT),
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THE REDUCTION OF INTUSSUSCEPTION IN CHILDREN BY BARIUM ENEMATA

The Radiologic and Clinical Signs Compared

by

Jens Munck Nordentoft

It is extremely rare in Denmark for children with intussusception to be subjected to primary operation without a preceding barium enema examination. If reduction of the intussusception is not accomplished by the enema, the child is operated on — most frequently without delay. It may be emphasized that the patients are almost invariably at once admitted to hospital where the surgeons refer them for roentgen examination. The appreciation of the results of conservative treatment is shown by the surgical and radiological collaboration, while the decision as to further therapeutic measures is taken by the surgeon.

Strangely enough, while this method has been used routinely in Denmark for many years, it seems still to be looked upon with some distrust in other countries. I have attempted elsewhere to explain the reasons for these different views. Possibly, one of the reasons is that clinicians may be inclined to attach greater weight to an improvement in the general condition of the patient than to the radiological signs of reduction, and this may lead to fatal results. I have repeatedly given strong warnings against taking the improved condition of the child after the administration of a barium enema as a reliable sign of reduction; powers of clinical observation and sound judgment are not enough, since the proof of success or failure of the reduction in all essentials depends on the radiological signs.

In his monograph (1943) written in English, STURE NYBORG tried to disprove my point of view that the improved condition of the child after barium enema treatment is a deceptive sign of reduction, stating that »a pronounced clinical improvement must be placed in direct con-

Submitted for publication, Oct. 30, 1951.

nection with successful reposition». When such a statement is published in a report from a children's hospital (the Surgical Department of Kronprinsessan Lovisa's Vårdanstalt in Stockholm) of high repute, the possibility cannot be ignored that it may cause members of the medical profession in other countries to attach too much importance to »the improved condition of the child».

For this reason, I wish to present evidence showing that the improved condition of the child after barium enema treatment is a dangerous sign of reduction.

Table 1 shows a brief abstract of the collective statistics from my monograph of 1943 (440 cases during the years 1928—1935); this publication appeared during World War II and unfortunately at that time it was not possible to include the case reports.

Table 1

Cases of intussusception in children during 1928—1935.

Total number	440	cases		
Barium enema treatment	197	»	25	deaths
Total number of secondary operations after barium enema treatment	100	»	23	»
of which *late secondary operations* (from about 5 hours to about 10 days after barium enema)	18	»	8	»

The following case reports are brief abstracts of the hospital records of these 18 cases, operated on more than 5 hours after the enema.

Report of Cases

Case 1. Girl, aged 3 months, with ileal intussusception between 12 and 24 hours old. *Barium enema:* Reduction from the left iliac fossa; a little barium passed into the ileum without filling it entirely. The patient went to sleep immediately after drinking milk-and-water. *Operation* (about 12 hours after admission): Ileal intussusception; 35 cm of the small intestine had to be resected. *Died* the next morning.

Case 2. Girl, aged 4½ months, with intussusception less than 12 hours old. *Barium enema* at 11 a. m.: intussusception in the left iliac fossa; the colon was filled; the tumor disappeared but reduction was doubtful. The child looked much better than before the enema, but at 5 p. m. was again screaming. *Operation:* disinvagination. *Died.*

Case 3. Girl, aged 5 months, with ileocolic intussusception 8 hours old. *Barium enema:* reduction from the rectum; the filling reached as far as the ascending colon. No tumor palpable. The general condition improved. The following evening the general condition was still fairly good, but there was high fever, and a further barium enema examination now showed intussusception in the descending colon. *Operation:* difficult disinvagination. *Died* the same day.

Case 4. Boy, aged 5½ months, had had signs of intussusception for about 24 hours; catarrhal with dry rales. *Barium enema* and manipulation under anesthesia. The

same evening the general condition was promising, but during the night the signs recurred and the next morning a tumor was again palpable. *Operation:* rather difficult disinvagination. High fever for four days postoperatively. Recovered.

Case 5. Boy, aged 6 months, with ileal-ileocolic intussusception 11 hours old. *Barium enema:* Typical intussusception in the transverse colon. The colon was filled, and the reduction believed complete. (NB.: Formation of annular figures outside the intussusceptum in the ileum.) The following morning nothing especially noteworthy, but 15 hours after admission the signs recurred. When the barium enema was repeated, the roentgen appearances were found to be the same as before. *Operation:* Intussusception arising from a point 12 cm above the ileocecal valve. Recovered.

Case 6. Boy, aged 6 months, with ileocolic intussusception 25 hours old. *Barium enema:* The intussusception was, according to the case record, easily reduced; cecum filled. The tumor disappeared and the patient fell asleep; but the next day there was high fever, bleeding from the rectum and a tumor in the abdomen. *Operation:* difficult reduction of an intussusception arising from the lower part of the ileum. *Died* the same day.

Case 7. Girl, aged 7 months. Onset of symptoms 27 hours previously. *Barium enema:* Reduction from the splenic flexure. A filling defect in the cecum was ascribed to edema (fig. 1). Next morning the child looked well but had fever (39.1° C.) and vomited. *Operation* 24 hours after admission: difficult disinvagination of an ileocolic intussusception. *Died* the same day.

Case 8. Boy, aged 8 months, was admitted with ileocolic intussusception 18 hours old; 5—6 hours previously the patient had been treated with a barium enema at another hospital, where it was believed that the intussusception had been reduced since the colon seemed to be filled. The patient was pale, critically ill and almost apathic. *Operation* (19 hours after the onset of symptoms): The reduction was easy but the patient *died* two days later.

Case 9. Girl, aged 9 months, with intussusception 24 hours old. *Barium enema:* The colon was rapidly filled and reduction was supposed to be successful, although the pattern of the cecum was not quite normal. After the enema the patient became quiet, but was a little languid and in the evening the symptoms recurred. *Operation* (6—7 hours after admission): Traces of a recent intussusception were disclosed, but there was no actual intussusception. Recovered.

Case 10. Girl, aged 9 months, with intussusception 14 hours old. *Barium enema:* Typical intussusception in the splenic flexure. The colon was filled, but a filling defect in the cecum persisted; it was believed to be due possibly to edema; an influx into the ileum was thought to have been observed (fig. 2). The patient was rather languid but did not seem to be in pain. *Operation* (5 hours later): 3 cm of the bowel was still invaginated; disinvagination was performed and the patient recovered.

Case 11. Boy, aged 10 months, with ileocolic-cecal intussusception (sanatio mirabilis!). *Barium enema:* A small filling defect was thought to be due to a residual intussusception or feces (fig. 3). After castor oil, much gas and copious greenish stools were passed during the following days. The patient was occasionally somewhat restless but otherwise nothing in particular was noticed. *A further enema* 5—6 days later revealed that a filling defect, about 3 cm in diameter, persisted, and the small intestine was seen to be dilated (probably subchronic intussusception). *Operation:* difficult reduction of

Fig. 1 (case 7). A considerable filling defect in the cecum is seen near the filled appendix. Reduction was considered likely, as the defective filling was thought to be due to edema. Operation about 24 hours later: an intussusception was disclosed and reduced. (Case of 1929, 2 years after the introduction of the barium enema method.)

Fig. 2 (case 10). Chestnut-sized filling defect at the ileocecal valve, which is directed proximally, the cecum and the ascending colon being displaced medially — signs not infrequently seen in infants; considered that the defect in the barium was possibly due to edema, but operation 5 hours later disclosed a small intussusception.

an edematous ileocolic intussusception. The patient slept very little for three days postoperatively; recovered.

Case 12. Boy, aged 11 months, with intussusception three hours old. *Barium enema:* Typical intussusception in the hepatic flexure. An attempt at reduction under fluoroscopic control revealed filling defects in the ascending colon suspected to be remnants of an intussusception. A striking transitory improvement of the general condition occurred. *Operation* (12 hours after admission): ileocolic intussusception arising 10 cm from the ileocecal valve. Recovered.

Case 13. Girl, aged 11 months, with intussusception about 24 hours old. *Barium enema:* reduction from the rectum to the right side, supposed to be complete, although a small tumor was still palpable; influx into the small intestine was believed to be observed. Five hours later the patient looked fairly well but the tumor had increased in size. *Operation* (7 hours after admission): An intussusception, the size of a hen's egg, was disinvaginated. Recovered.

Case 14. Boy, aged 14 months. *Barium enema:* Apparent reduction of an ileocolic intussusception, 12 hours old. It was believed that the enema had passed into the small intestine, but there was some doubt as to whether complete reduction had been effected.

Fig. 3 (case 11). A filling defect, about 3 cm in diameter, is seen close to the filled appendix; presumed due to edema after the reduction of the intussusception. A further enema 6 days later showed similar appearances. The patient was operated on — and recovered (case of 1931).

The patient improved and fell asleep. Next afternoon he became ashy pale and began to scream. *Operation* (about 20 hours after admission): disinvagination of a gangrenous ileocolic intussusception. *Died* the following day. (The collapsed sigmoid colon had been mistaken for the small intestine.)

Case 15. Girl, aged 16 months, with intussusception *5 days old* (no tumor palpable). *Barium enema:* Only the rectum and the sigmoid colon were filled, the enema then being evacuated. The patient was quiet during the night; no vomiting or palpable tumor. *Operation* (next day): an intussusception, 10—15 cm in length, was easily reduced. Recovered.

Case 16. Boy, aged 4 years, with ileocolic intussusception about 48 hours old. *Barium enema:* no definite signs of intussusception; the cecum apparently filled. The patient fell asleep, but the next morning the signs recurred. *Operation* (about 18 hours after admission): An intussusception of the ileum, 5—6 cm in length, was quite unexpectedly disclosed. Recovered.

Case 17. Boy, aged 4 years, with ileocolic intussusception 4 days old. *Barium enema:* A filling defect in the cecum was thought to be due to feces or a tumor. On the following day copious stools were passed, but *six days later* the abdomen was meteoristic with visible peristalsis. *Operation* (ileocolic intussusception, Meckel's diverticulum): enterostomy. *Died* the same day.

Case 18. Boy, aged 4 years. The patient had previously had intussusception twice and had been treated by means of a barium enema; no operation. *Now* intussusception four hours old. *Barium enema:* Typical figure in the splenic flexure; the colon was apparently filled (the appearances were much like those shown in figure 118 in the author's monograph (4). Three days later the patient was stated to be in an excellent general condition. *Operation* (9 days after admission): no intussusception but a Meckel's diverticulum found; resection of the small intestine. Recovered.

As may be seen from the case reports, clinical improvement following the barium enema is mentioned in nearly all the cases. In some cases the improvement was very pronounced (1, 2, 3, 6, 12, 14, 15); in others it is expressed less distinctly, sometimes merely by stating that nothing in particular was noticed (4, 5, 7, 9, 10, 13, 16, 18). In one case (8) the general condition after the barium enema is not mentioned. Finally, two cases (11, 17) presented unusual pictures which are rather difficult to interpret. Some form of »clinical improvement» must, however, be presumed to have been present in at least 15 of the 18 cases.

The radiologic signs of reduction, *i. e.* a well-filled cecum and distinct influx into the small intestine, were not unmistakably present in the cases reported, but it must be borne in mind that the cases are rather old and from the years immediately following the introduction of the barium enema method; at the present time a far higher degree of certainty in reduction would be demanded — otherwise surgical measures would immediately be resorted to.

A closer analysis of the radiologic signs is not attempted here; such an analysis may be found in my monograph published as Acta Radiologica, Supplementum LI[3]. Roentgenograms with pertinent legends illustrating some of the above-mentioned cases are published in the monograph as follows: Case 1: figs. 73—74; case 5: figs. 93—94; case 6: figs. 21—22; case 12: fig. 106; case 14: figs. 95—100; case 16: fig. 108; case 17: figs. 101—102, and case 18: figs. 117—118. These illustrations and figs. 1—3 in this paper represent all existing roentgen films of the ileocecal regions in the 18 cases of intussusception now reported.

The conclusion of this investigation must therefore be that pronounced clinical improvement *cannot* »be placed in direct connection with successful reposition». It is dangerous to regard the improvement of the general condition of the child following a barium enema as a reliable sign of reduction.

SUMMARY

A series of case reports, following a previous publication show that the radiologic signs of reduction must be considered of decisive importance in the barium enema treatment of intussusception in children; on the other hand, the clinical signs — notably an improvement in the general condition following the enema — are only of minor importance; it is dangerous to regard the latter as reliable signs of reduction.

ZUSAMMENFASSUNG

Der Bericht über eine Reihe von Fällen im Anschluss an eine frühere Veröffentlichung zeigt, dass die röntgenologischen Kennzeichen der Reposition als von entscheidender Bedeutung für die Behandlung der Invagination im Kindesalter mit Kontrasteinlauf angesehen werden müssen; andererseits sind die klinischen Anzeichen- — besonders eine Verbesserung des Allgemeinbefindens im Anschluss an den Einlauf — nur von geringerer Bedeutung. Es ist gefährlich, letztere als ein zuverlässiges Zeichen der Reposition zu betrachten.

RÉSUMÉ

Une série d'observations, faisant suite à une publication précédente, montre que les signes radiologiques de réduction doivent être considérés comme décisifs dans le traitement par lavement baryté de l'invagination intestinale chez l'enfant. D'autre part, les signes cliniques, entre autres une amélioration de l'état général à la suite du lavement, ne sont que d'une importance secondaire; il est dangereux de les considérer comme des signes certains de réduction de l'invagination.

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FROM THE ROENTGEN-DIAGNOSTIC DEPARTMENT (DIRECTOR: OLLE OLSSON) OF THE UNIVERSITY CLINICS OF LUND, SWEDEN

THE CAPACITY OF THE LARGE INTESTINE

by

Olle Olsson

The anatomy of the large intestine varies widely. These variations, particularly as to length and disposition in the abdomen have received much attention. Some authors have claimed that an etiologic relationship exists between certain symptoms and irregularities or abnormalities seen. This is evidenced, for example, by such terms as dolichocolon and redundancy of the colon. Numerous papers witness the attempts made to give clinical significance to this wide range of variations.

Like the stomach, the large intestine serves to a certain extent as a reservoir in the digestive process. Broadly speaking, the proximal half of the large bowel may be regarded as an absorptive organ, the distal half as an organ of defecation. During the two phases of digestion represented by these functions, each half acts as a reservoir, the right half for the storage of ingesta passed on for further absorption from the small intestine, the left half for the storage of waste products pending discharge. Viewed from this angle, the *capacity of the large bowel* is of *anatomical* and *functional* significance. From a clinical point of view this significance is accentuated by the fact that certain pathologic processes are accompanied by a disturbance of the storage capacity of the large bowel. It is therefore remarkable that the study of the capacity of the large bowel should have been outshadowed to such a degree by observations of other anatomic features of this organ. This neglect is still more remarkable in the light of the fact that the capacity of the large gut may be readily determined under simple conditions by measuring the amount of contrast fluid employed for the opaque enema in the ordinary roentgen examination of the large intestine.

Submitted for publication, Nov. 1, 1951.

Earlier Studies of the Capacity of the Large Intestine

A number of isolated and more or less exact figures of the quantity of contrast fluid necessary to fill the large gut satisfactorily for roentgen purposes are available in the literature on megacolon. Reports of systematic studies of the capacity of the large bowel are, however, scanty.

In a postmortem investigation carried out on soldiers, BROSCH (1912) found the capacity to range from 1,500 cc. to 2,500 cc. and rarely to exceed 4,500 cc.

DRUMMOND (1914) studied a few cases postmortem and reported a capacity of 2—2.5 pints (about 1—1.5 litres). He also observed that for a rectally injected fluid to reach the caecum, it was necessary to employ about 800 cc.—1,100 cc.

In a paper on the pressure conditions prevalent in the large gut, JOLTRAIN, BAUFLE & COOPE (1920) stated that 1,500 cc. fluid is always sufficient to fill the organ. In a textbook description of the large bowel BOCKUS & Coll. (1947) write »The amount necessary to fill the colon varies greatly in otherwise normal subjects. The average is about 36 ounces (1,065 cc.).»

MEYER (1932) was the only researcher to study the question in a large series of cases. One hundred hospital patients chosen at random were given ordinary water enemata. The application pressure, which was gentle, was not removed until the patient reported a feeling of tenesmus. In 45 of the patients the sufficiency of the ileocaecal valve was checked roentgenographically. In all except one, the degree of sufficiency was considered satisfactory for the measurement of the capacity of the large gut. The capacity measured was usually 1,500 cc.—2,500 cc. in women and 2,500 cc.—3,000 cc. in men. These figures must, however, be accepted with reserve because the examination technique, as apparent rom the brief description, was fairly crude.

It will be obvious from the above that our knowledge of the capacity of the large intestine is imperfect. In the belief that an elucidation of the question would be of definite value, the capacity of the large bowel of a number of patients was, some years ago, determined in association with the roentgenologic examination of the colon.

Author's Series

The capacity of the large bowel was determined in 350 adult patients of whom 148 were men and 202, women. The patients' ages ranged from 19 to 85 years; 126 of the patients were not more than 50 years of age. All the subjects examined were hospital patients. The study was thus not carried out on »normals» in the restricted sense of the word.

The present series was selected from those patients referred to our department for roentgen examination of the colon. Physicians in the other departments were requested to refer patients to our department for the slightest indications so that it might be possible to collect a series of »normals». Even in the absence of such a request the range of general indications must be kept wide on account of the vagueness of symptoms as, for instance, in cancer of the colon.

In the present study the »normals» consisted of a selection of patients without symptoms of colonic disease. These patients had been referred to the department on account of general symptoms such as anaemia, loss of weight, loss of appetite, etc. Another group of patients were suffering from diseases (cholelithiasis, spondylosis deformans, etc.) accounting for their symptoms but not excluding the co-existence of other causal factors. Finally there were also a number of patients with diffuse abdominal symptoms not necessarily colonic in nature. All these three subgroups were referred to our department on account of such a wide range of indications that the subjects selected for inclusion in the present series were practically »normal». The first group comprised 121 patients.

A second group consisted of 178 patients with varying and often only slight constipation; only a few of these patients were referred to the roentgen department on account of constipation; the majority belonged to the aforementioned subgroups; they have been separated off here as there had been a history of constipation.

Finally there was a small group of 51 patients that had sought relief for diarrhoea, transient or persistent, recent or long-standing and of varying degree.

All patients with stenosis due to tumour, inflammation or other pathologic process were excluded. None of the patients included had signs of abdominal tumours or constrictive processes originating in or encroaching upon the bowel.

The history, especially as regards defecation, was taken of all of the patients included in the present series. Furthermore, only patients with ordinary dietetic habits were accepted.

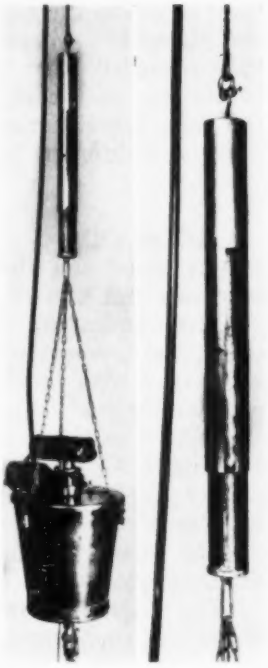
Examination Technique

The usual technique was applied, *i. e.* opaque enema under fluoroscopic control, and radiography. The contrast fluid was administered with the aid of a can devised by HELLMER (1939). The device was now complemented with a meter, consisting of a spring balance from which the can was suspended (Figs. 1 a and b). The scale was graduated in such a manner that 1 cm. on the scale corresponds to $^1/_2$ litre contrast

fluid. The can was always suspended at a constant level corresponding to an application pressure of 0.75 m.; this was fairly constant throughout the administration because the falling level of the fluid was compensated by a corresponding automatic rise in the level of the can itself.

The contrast fluid was prepared in a uniform manner and was of one and the same specific weight throughout the investigation. The temperature of the contrast fluid was maintained at a constant temperature of 38° by means of a thermostat. Continuous rotation by an electric uniter prevented sedimentation.

All of the patients were prepared for examination in the same manner, namely by means of castor oil in the morning, and a water enema in the evening of the day before the examination and a second water enema on the morning of the examination.



a. b.

Fig. 1. Container suspended from a spring balance.

The contrast fluid was administered in the usual way, *i. e.* rather gently and under fluoroscopic observation. As soon as the fluid had reached the caecal pole the weight was read. At this stage the fluid usually began to pass into the small intestine. In some cases, however, the ileocaecal valve tolerated so much pressure that up to 1 litre could be administered after the fluid had reached the caecal pole; the ordinary filling and not the maximal filling was registered. Thus, the term »capacity» of the large intestine as used here is to be understood as the capacity assessed in the manner described above.

Repeated examinations of the same patient but by different examiners produced practically equal values.

After being examined horizontally the patient was screened in the erect position in order to control the extent to which the bowel had been filled. If the filling is incomplete the intestinal gas will be entrapped in the flexures, where it is easily recognized. Patients in whom this check showed the filling to be incomplete were excluded as were those in whom the gut had not been completely voided before examination and therefore still contained scybala. The control of the first factor, the degree of filling in the erect position often revealed small accumula-

tions of gas in the flexures. In some cases the accumulations were large and therefore suggested that the filling was inadequate. These patients were excluded from the series. This point is worth remembering and emphasizes the necessity of careful palpation of the various sections of the large bowel during fluoroscopy and also of an examination of the patient in different postures.

Results

The quantity of opaque fluid necessary for filling the large bowel was recorded and the sex noted. Entries were made not only of the »normals» but also of patients with diarrhoea and with constipation.

In an endeavour to find a norm for evaluating the capacity of the colon, the amount of opaque solution administered was compared in every case with the height and surface area of the patient; no certain relationship was found.

In view of the known tendency to constipation and decreasing tonus of the smooth muscle with advancing age, the size of the large gut of elderly people was compared with that of younger individuals; no definite difference was observed.

The capacity measured in every case was therefore recorded as an absolute quantity.

The diagram shows that the deviation of the cases in every group is very large. Among the normals the quantity necessary to fill the colon varied between 0.6 and 3.0 litres, the average being 1.45 litres.

In the constipated group the corresponding figures were 0.7 and 3.9 litres with an average of 1.74.

Among the patients with diarrhoea the values recorded varied between 0.4 and 2.5 litres with an average of 1.38 litres.

The average capacity of the bowel in the normal males was 1.50 litres; in the normal females it was 1.40 litres. The corresponding figures for the constipated group were 1.9 and 1.57 respectively. Neither in the constipated group nor in the normal group did the sexes differ as regards the average capacity of the large bowel. The statistical differences observed were not greater than once the standard deviation. Nor was there any such difference between the normal group and the constipated group. The greatest difference was found between the men in the normal group and those in the constipated group, but even there it was not significant.

The number of colonic examinations indicated by diarrhoea was too small to permit of statistical analysis. It will be readily seen from the table, however, that the lowest values of the entire series are in this group, which as whole shows a shift to the left. The lowest values were found in patients with serious ulcerative colitis.

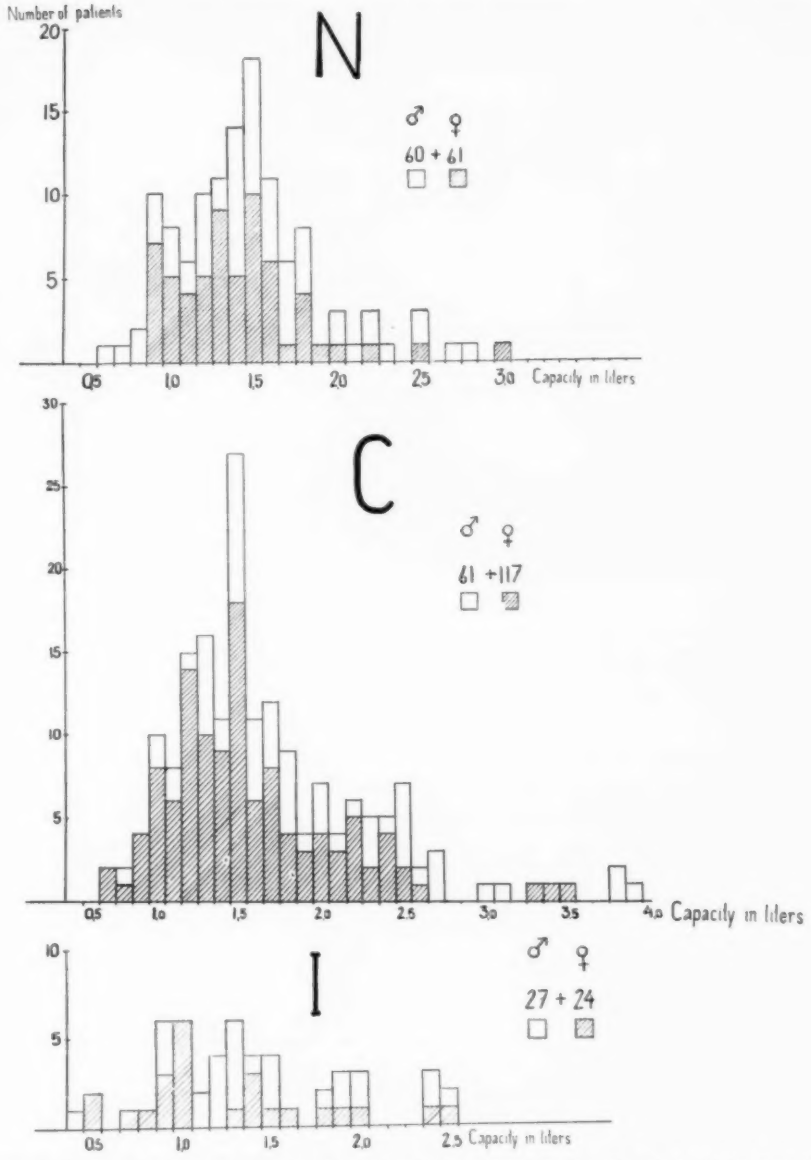
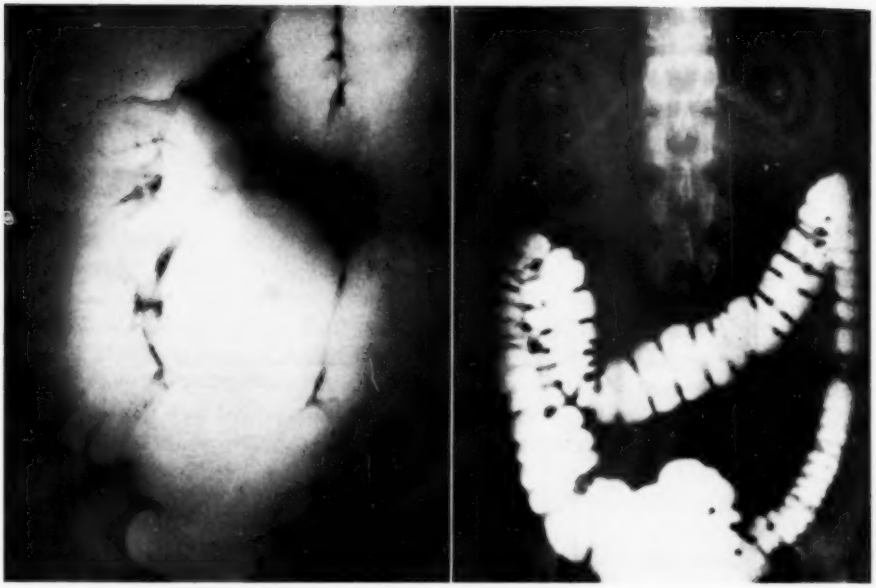


Diagram showing the number of patients and the capacity (litres) of the large bowel in the »normal» group (N), in the constipated group (C) and in those with diärrhoea (I). The columns representing the males and the females are superimposed.



a. b.

Fig. 2. The two extremes in the constipated group.
a) man with slight constipation and a large bowel capacity of 3.75 litres.
b) woman with moderate constipation and a corresponding capacity of 0.7 litre.

The study showed to what a great extent the capacity of the large bowel varies from one person to another. It also showed that the clinical interpretation of the capacity recorded must be made on the merits of each case separately. A knowledge of the capacity of the large bowel must be valuable to the clinician for several reasons.

The roentgenologist's report of the capacity of the bowel enables the clinician to form a much more definite opinion of the anatomy of the organ than does a general description of its length, thickness and tortuousness.

In the treatment of a patient for constipation it must also be of clinical importance to know the capacity of the large gut. The two extremes in the present series were a young man with slight constipation and a large bowel capacity of 3.75 litres (Fig. 2 a) and a woman with moderate constipation and a corresponding capacity of 0.7 litre (Fig. 2 b). That these differences indicate different types of treatment is obvious, although it should not be necessary to resort to extremes to exemplify the statement.

In the treatment of colitis knowledge of the quantity of opaque fluid necessary to fill the large bowel is useful in estimating the degree of the change and thereby provide a valuable complement to the general clinical picture. In the conservative treatment of ulcerative colitis a possible change in the capacity of the bowel will undoubtedly be of value in judging the results of treatment.

In the diagnosis of megacolon knowledge of the capacity of the large bowel will also serve to complement the radiologist's report. Here, too, it might be of interest to check the capacity for possible changes during the treatment of the condition.

The clinical value of such roentgenologic information may be discussed from several points of view, but the present series was too small to warrant further considerations. The purpose of this study is to stimulate the registration and clinical utilization of information easily obtainable during the routine examinations of the large intestine.

SUMMARY

The capacity of the large bowel was measured in association with contrast enema examinations. The amount of contrast fluid necessary for filling the organ was determined. The values obtained are tabulated and discussed.

ZUSAMMENFASSUNG

Das Fassungsvermögen des Dickdarmes bei röntgenologischen Kontrastuntersuchungen dieses Darmabschnittes wurde bestimmt. Die Menge Kontrastflüssigkeit, die zur völligen Ausfüllung des Dickdarmes nötig war, wurde ermittelt. Die Werte wurden tabellenmässig aufgestellt und diskutiert.

RÉSUMÉ

La capacité du gros intestin a été mesurée au cours d'examens par lavement opaque. La quantité de liquide opaque nécessaire pour remplir l'organe est déterminée. Les chiffres obtenus sont classés et discutés.

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FROM THE DEPARTMENT OF ROENTGENOLOGY (DIRECTOR: GÍSLI FR. PETERSEN),
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ATHEROSCLEROSIS OF THE ABDOMINAL AORTA

A Roentgenologic Study

by

Gísli Fr. Petersen

More or less marked evidence of calcification of the abdominal aorta is no uncommon finding in advanced age, particularly in routine roentgenography of the lumbar column. These findings are usually accidental, the films being obtained for some other purpose. Most interest has been displayed up to now in the thoracic aorta owing to its easy access to investigation by roentgen rays, but recent technical advances have improved the conditions for examining the abdominal portion. Calcification, even if only localized, may often be observed. Aortic atherosclerosis is usually most strikingly prominent in the abdominal portion. This observation as well as the increasing interest in the roentgenology of the arterial system make it reasonable to pay more attention than previously to the abdominal as well as the thoracic aorta in atherosclerosis of the central arteries.

The pathological tissue changes which form a syndrome must be borne in mind by roentgenologist and clinician alike. Dilatation of the thoracic aorta does not afford sufficient evidence for a diagnosis of atherosclerosis. The roentgen diagnosis is based on calcification which appears in the form of major or minor patches or plaques. After the age of forty, one can expect initial senile, presumably physiological, changes in the aorta as well as in other tissues of the body. The aortic wall undergoes induration and thickening owing to an increase in collagen connective tissue, mainly in the tunica intima. Elastic tissue, on the other hand, grows less conspicuous. The vessel begins to yield to the pressure of the column of blood, widening and lengthening, and the arch of the aorta becomes prominent. These tissue changes, which have been named

Submitted for publication, Sept. 28, 1951.

senile fibrosis (ASCHOFF), probably represent normal senile degeneration without any definite relationship to aortic atherosclerosis.

The dilatation, as seen on the roentgen film, may become quite considerable. According to pathological findings, the circumference of the base of the aorta may increase from 50 mm to 70 mm or even more. Clinical and roentgenological interest has been directed toward the thoracic aorta, and the significance of diffuse dilatation has often been exaggerated. If the roentgen film does not reveal calcification, no conclusion can be drawn as to atherosclerotic changes in the vessel, even though it may be dilated.

The factor of most interest in connection with arteriosclerotic changes of the aorta is *calcification* which is the roentgenologic manifestation of arteriosclerosis and of the distribution of the process in the vessel. The aorta is an artery of elastic type, *i. e.* elastic tissue predominates in the tunica media which contains comparatively few muscular fibres. Arteriosclerotic changes are situated mainly in the intima which may exhibit atheroma with fibroid changes, calcification, and sometimes ulceration. These phenomena are classified as *atherosclerosis*, »arteriosclerosis» being used in a wider sense. The process may also involve the media to a varying extent, particularly in advanced cases. In atherosclerosis, aortic calcification may vary considerably, manifesting itself in the form of small, diffuse calcium granules, patches or calcified plaques of irregular shape and differing in thickness and size. Calcification is seldom confined to the media without involving the intima or at least without having formed atheromatous changes in the latter. *Thus, if a roentgen examination shows calcareous shadows in the aorta, it may usually be concluded that atherosclerosis is present in the intima.*

Situation. Aortic atherosclerosis affects mainly the abdominal portion of the aorta at the outset, usually immediately above the bifurcation; the process not infrequently reaches down into the common iliac arteries. Calcium plaques may often be observed where the aorta gives off its large abdominal branches. In the thoracic portion the process affects mainly the arch of the aorta, the base of the ascending portion, and the region of the intercostal arteries. In 14 cases we obtained both radiologic studies of the abdominal aorta in vivo and post-mortem reports. In eight of these cases the vessel was removed, cut open in its entire length and roentgenographed. This gave a clear representation of the situation and distribution of the calcification. Naturally, the calcification usually proves rather more marked and widespread than indicated by the roentgen films obtained in vivo. The roentgen findings also show more calcium than can be detected by macroscopic inspection and palpation of the artery. A compact plaque of calcium, about 1 cm in diameter and situated in a typical site, ought usually to be visible. Should the calcification be

located only superiorly, at major abdominal branches, or confined to the common iliac arteries, the roentgen findings may be uncertain or negative. On the other hand, calcareous patches in a regular row may sometimes be observed where the aorta gives off branches lying anterior to the lumbar column (Fig. 4). Of course, technique and the thickness of the subject play rôles in this connection.

It is not out of place to mention arteriosclerotic changes and their type in the various aortic branches. Some authors consider the coronary arteries to be of muscular type, whereas others (WOLKOFF, DIETRICH) have expressed the opinion that major branches also show the structural peculiarities of elastic arteries. The intima is composed of 3 layers, just like the aortic intima. Arteriosclerotic changes are reported to be similar to those of the aorta, *i. e.* atherosclerosis although medial calcification is not likely to be present. RÜHL found atherosclerosis of the aorta comparatively often with coronary sclerosis. Although elective affection of the coronary arteries is sometimes observed, calcification of the aorta may be interpreted as a sign supporting a suspicion of coronary sclerosis. The hypogastric arteries are the abdominal branches most often affected with atherosclerosis. In the mesenteric and splenic arteries, calcification of the media is considered more common. Atherosclerotic changes may extend quite far down the common iliac arteries and even be found in the femoral and crural arteries (RÜHL, LINDBOM), although the latter more often show calcification of the media, like other arteries of muscular type. It might therefore be considered desirable to obtain films of the abdominal aorta in circulatory disturbances of the lower limbs, although arteriography is the diagnostic method of choice in such conditions.

Radiographic Technique. The subject is placed in the left horizontal position and tilted 45° dorsally. The central ray is directed through the crest of the ilium, about 5—6 cm in front of the spina anterior superior. (The oblique projection was recommended by AKERLUND at the Congress of the Northern Association for Medical Radiology in Copenhagen 1927.) In this position, the abdominal aorta is closest to the film and may be traced farther down than in a true lateral view. It is projected anterior to the vertebral column, but its posterior margin may sometimes be superimposed upon the vertebral column. The bifurcation usually lies at the level of the lower margin of the 4th lumbar vertebra; it is sometimes situated at the level of the 5th lumbar vertebra in which case it becomes superimposed upon the wing of the sacral or iliac bone.

The radiologic literature contains comparatively few references to calcification of the abdominal aorta. LEDOUX-LEBARD and co-workers collected 50 cases and others have published a few or single cases, usually in connection with various clinical characteristics which they have related to aortic calcification.

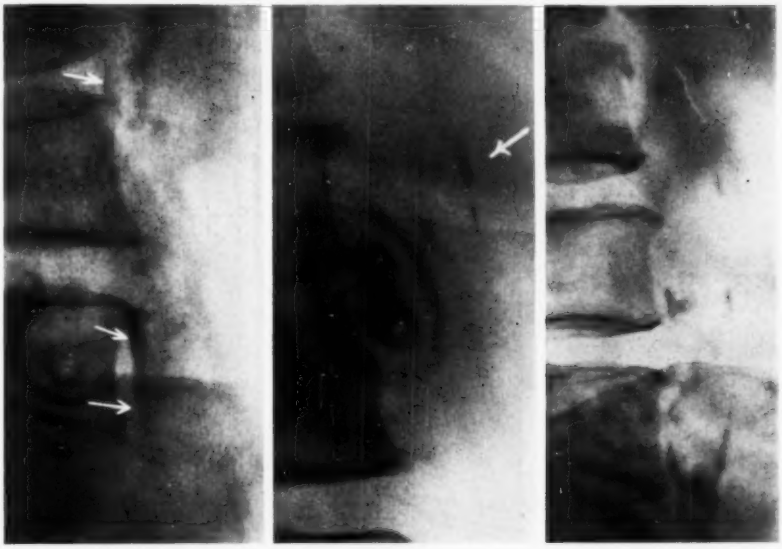

Fig. 1. Fig. 2. Fig. 3.

Fig. 1. Stage I calcification in the posterior wall of the aorta above the bifurcation at the level of the 4th lumbar vertebra. Vague calcareous patches, superiorly.

Fig. 2. Stage I calcification in the anterior aortic wall.

Fig. 3. Stage II calcification. Dense calcareous shadow at the bifurcation. Calcareous shadows in pairs, superiorly.

The roentgen appearances of calcification of the abdominal aorta may be quite varied, according to the stage and spread of the lesion. Calcareous patches in the aorta are most clearly visible when the central ray hits them tangentially and they appear as contour shadows, on the posterior or anterior wall or both. These linear shadows are usually dense and well-defined, but may also show a less marked contrast and irregular contour facing the vascular lumen. The shadows may be single or arranged in a row so as to outline the contours of the vessel. They are often interspersed with irregular patches of calcium which may at times be the outstanding feature. Initial calcification often occurs inmediately above the bifurcation which may present a typical, funnel-shaped shadow, tapering downwards. It is dense and well-defined towards the vertebral column if the calcification affects mainly the posterior wall (Fig. 1). If the calcification be more advanced, the films may reveal a very dense and compact elongated shadow at the bifurcation and at the same time calcified patches lying superiorly (Fig. 3). As a rule, the diagnosis of

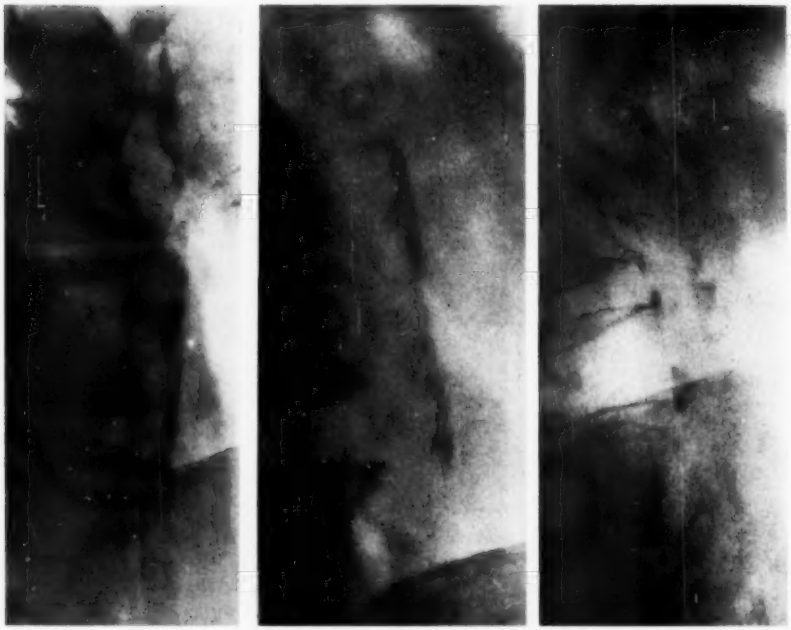

Fig. 4. Fig. 5. Fig. 6.

Fig. 4. Female, aged 59, with attacks of abdominal pain and hypertension. Stage II calcification of the abdominal aorta throughout its course and of the common iliac arteries.

Fig. 5. Female, aged 63, with attacks of abdominal pain and hypertension. Stage II calcification, mainly affecting the anterior aortic wall.

Fig. 6. Female, aged 63, with arrhythmia and hypertension. Stage II calcification, linear shadows and irregular plaques.

calcification of the abdominal aorta is easy, particularly in the presence of typical linear shadows. A situation and distribution anterior to and along the lumbar column is typical. The calibre of the vessel may often be measured when calcification appears in both the anterior and posterior walls. The differential diagnosis will have to be made from calcification of lymph nodes and abscesses, of hydatid cysts in the liver and peritoneum and possibly of vertebral ligaments; these may all at times present similar appearances.

Aortic calcification may occur in *2 stages* according to its severity or extent: Stage I: single elongated shadows of calcium or single calcareous patches in a typical site. A calcareous shadow exceeding 1 cm is considered positive. Stage II: calcified shadows in both the anterior

and posterior walls. Occasionally, irregular calcification affecting a large area, or calcification throughout the entire course of the vessel.

Incidence. In serial examinations of 220 patients, 101 females and 119 males, the incidence and stage of aortic calcification in age groups and sexes was as follows:

Females:

Age 40—49 (10):	2	positive,	Stage	I			
50—59 (32):	11	»	»	I: 6,	Stage	II:	5
60—69 (34):	18	»	»	I: 7,	»	II:	11
70—79 (19):	13	»	»	I: 4,	»	II:	9
80—89 (6):	5	»	»	I: 1,	»	II:	4.

Males:

Age 40—49 (15):	0	positive,					
50—59 (37):	3	»	Stage	I: 1,	Stage	II:	2
60—69 (39):	9	»	»	I: 5,	»	II:	4
70—79 (25):	11	»	»	I: 6,	»	II:	5
80—89 (3):	1	»	»	I.			

A total of 49 females out of 101 were positive, *i. e.* 48.5 % as compared with 24 males out of 119, *i. e.* 20.2 %. Sex difference 28.34 % ± 6.4.

The material is unselected, consisting of in-patients as well as out-patients, referred to us for various diseases. The figures therefore do not perhaps give a correct impression of the incidence of aortic calcification in completely »healthy» subjects, *i. e.* in subjects unaffected with diseases which may influence or predispose to atherosclerosis. It is a matter of experience, however, that after middle life »healthy» is often reduced to a relative concept, and it proves difficult to select such subjects.

As apparent from the table, roentgen evidence of aortic calcification may be expected chiefly about and after the age of fifty. The female predominance is striking and has been confirmed by our subsequent observations. In evaluating the results, however, it must be borne in mind that the roentgen film shows only one aspect of atherosclerosis, *i. e.* calcification. Some reserve must be exercised in assessing the reliability of calcification as an indicator of other aspects of the disease in the aorta and its branches, particularly atheromatous changes and intimal thickening; the aorta may be affected with considerable atheromatosis without exhibiting calcification worth mentioning. Nevertheless, it is worth considering the *clinical significance* of discovering aortic calcification on roentgen examination. According to LEDOUX-LEBARD, FELDMAN, and others, atherosclerosis in the abdominal aorta may give rise to clinical symptoms. Arterial spasm and circulatory disturbances in the abdominal arteries may cause pain, sometimes quite severe (*angina abdominis*). Ten of the patients under discussion complained of attacks of abdominal pain, sometimes situated in the epigastrium and occasionally radiating to the back, the sacrum or even the lower limbs. In the absence of any other

explanation of such abdominal pain, it is not unreasonable to presume that it was due to vascular spasm. The attacks would persist for some time, even a few hours, and subside either suddenly or gradually.

Fig. 4 shows unusually marked calcification. For the previous 10 years the patient had suffered from attacks of severe pain in the lower abdomen, sacrum, and thighs. The attacks would come on suddenly, usually persist for a few hours and then cease or slowly subside. The main symptoms were accompanied by headache and dizziness. Neither the history nor the clinical examination gave any clue as to the nature of the condition. The patient had hypertension, 230/120 mm of mercury; following treatment, the blood pressure decreased to 155/95—170/110 and at the same time the pain and other symptoms disappeared.

Where there is suspicion of *arteriosclerotic heart disease*, particularly in subjects of about fifty years of age or over, the roentgen examination of the heart and thoracic aorta ought to be supplemented by a study of the abdominal aorta. Calcification of the latter may afford information about the state of the central arteries, and in cases of doubt it may prove helpful in diagnosing heart disease. Arteriosclerosis often selectively affects certain arterial systems, such as the one formed by the cardiac vessels. Coronary sclerosis is considered perceptibly more common in males than females, but so far the reason is not known. Among 17 cases (7 females and 10 males) diagnosed clinically as cardiac myodegeneration, coronary sclerosis, or having suggestions of organic changes in the cardiac vessels, 7 (4 females and 3 males) exhibited calcification of the aorta. These figures are too small to form the basis of conclusions and the problem calls for further study. Fig. 5 shows high-grade calcification of the aorta. Clinical diagnosis: Cardiac myodegeneration, hypertension (196/100 mm of mercury). Heart of normal size, but dilatation of the thoracic aorta without signs of calcification. In addition to the cardiac symptoms, the patient suffered from attacks of pain in the lower abdomen, radiating down into the thighs.

A correlation is apparent between calcification of the abdominal aorta and *hypertension* ($\geqq$ 160 mm of mercury). Among 73 patients with aortic calcification, hypertension was found in 52 (71.2 %), whereas among 147 patients without calcification, hypertension occurred in 50 (34 %). The theoretical likelihood of coincidence without any correlation is calculated as 35.9, but aortic calcification co-existed with hypertension in 52 ± 5.5 cases. Classification into age groups also shows a distinct difference between theoretical and observed coincidence.

From among the entire series of 307 patients, the females exhibited hypertension in 54.5 % as compared with 31.7 % in the males.

It seems advisable to submit patients about and after middle age to roentgen examination of the abdominal aorta in the presence of: At-

tacks of abdominal pain of obscure etiology, suspicion of heart disease of arteriosclerotic origin, hypertension and lastly, as a link in an examination of the vascular system preparatory to major operation.

SUMMARY

The communication is mainly a continuation of the author's earlier paper on the subject (see References). An account is given of the incidence of calcification of the abdominal aorta in 220 patients, ranging in age from 40 to 90. The significance of roentgenography of the abdominal aorta is pointed out.

ZUSAMMENFASSUNG

Die Veröffentlichung besteht in der Hauptsache aus der Fortsetzung einer früheren Arbeit des Verf:s über das gleiche Thema (siehe Literaturübersicht). Ein Bericht über das Vorkommen von Verkalkungen in der Aorta abdominalis bei 220 Patienten im Alter von 40—90 Jahren wird abgegeben. Die Bedeutung der Röntgenuntersuchung der Aorta abdominalis wird hervorgehoben.

RÉSUMÉ

La note constitue essentiellement la suite des précédents articles de l'auteur sur le même sujet (voyez la bibliographie). La présence de calcifications au niveau de l'aorte abdominale est signalée chez 220 malades âgés de 40 à 90 ans. L'importance de la radiographie de l'aorte abdominale est mise en évidence.

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FROM THE RADIOLOGICAL CLINIC (DIRECTOR: B. REFSLUND POULSEN), CENTRAL HOSPITAL, ESBJERG, DENMARK

ROENTGEN TREATMENT OF BRONCHIAL ASTHMA

by

B. Refslund Poulsen

The use of roentgen rays in the treatment of bronchial asthma is by no means new. Several authors have reported good results from irradiation of the thorax. The most comprehensive case material is that of LEDDY and MAYTUM, who in their most recent survey present more than 1,000 cases which were treated with low-dosage roentgen irradiation of the thorax. In 85 per cent of their cases a more or less pronounced beneficial effect was observed, while no, or only a doubtful, result was obtained in the remaining 15 per cent. As a critical review of the results obtained by other investigators is embodied in the aforementioned study, the reader is referred to this for the historical aspects of the subject.

The author is under the impression that the palliation which may be obtained by roentgen treatment of asthma is utilized in this country to a smaller extent than it deserves, for which reason the following series of cases, although rather limited, is presented. At the Central Hospital in Esbjerg, which serves a district with a high incidence of asthma owing to the rather boisterous climate of the West coast, we took up this method of treatment on the suggestion of the general practitioners, who after having exhausted all available therapeutic means requested us, as a last resort, to try roentgen treatment. The striking beneficial effect obtained in the first two patients with bronchial asthma treated became known among doctors and patients in the district, and we now often see patients who have requested their doctor to refer them to the Radiological Clinic for roentgen treatment.

Technique

The roentgen rays are delivered at 160 kv., with filtration through 0.5 mm Cu and 1.0 mm Al, at a distance of 30 cm. The size of the radia-

Submitted for publication, Oct. 30, 1951.

tion field is 16 × 10 cm. All patients receive treatment over four fields, viz. two anterior and two posterior fields, directed to the right and left hilar regions, respectively. By using the said size of field and distance the entire hilar region and the greater part of the lungs are irradiated. The dosage has been 100 r × 4 to each of the fields, administered with two treatments at a time (for example, the right and left anterior fields) every other day. — In most cases, the course of treatment was completed in the course of about 18 days. The majority of the patients received the full treatment; a few interrupted the course when they had received 300 r to each field, either because they were satisfied with the result or for reasons irrelevant to their disease. A few of the patients were hospitalized during treatment, but most of them were treated as out-patients. No untoward effects were noticed, and none of the patients complained of radiation sickness.

Fifty-three patients were treated. Of these, information regarding the results was obtained in 48 cases. Most of the patients were asked to present themselves for a follow-up examination two months after the completion of the treatment, and a few gave information as to the results by letter.

Practically all the patients suffered from severe chronic bronchial asthma of a duration ranging from 3 months to 3 years or more; all the other common therapeutic aids had been tried.

Table 1

Age distribution of the patients

Age, in years	0—10	10—20	20—30	30—40	40—50	50—60	60—70	>70
Women			1	5	8	7	3	
Men		1		6	3	4	8	2
Total		1	1	11	11	11	11	2

Table 2

Duration of the disease

Years	½	½—1	1—2	2—5	5—10	10—20	>20
Women	4		2	5	4	6	3
Men			1	3	1	11	8
Total	4		3	8	5	17	11

The results of the treatment are shown in table 3. In questioning the patients an attempt was made to avoid any exaggeration of the effects of the treatment, and no leading questions were asked. Patients with no improvement in the frequency and intensity of asthmatic attacks were classified as unchanged. It may be noted that none of the patients complained of aggravation of the disease after treatment. Those who

stated that their attacks had definitely decreased in frequency and intensity were grouped as improved. In this group we also included patients who had had only very mild occasional attacks. Those who had had no attacks during the period from shortly after the completion of the treatment to the follow-up examination two months later were grouped as considerably improved.

Table 3

Results of roentgen treatment

	Unchanged	Improved	Considerably improved
Women	5	9	10
Men	3	13	8
Total	8	22	18

The time of the onset of improvement was fairly constant. Some of the patients noticed relief before the end of treatment, but in most cases the improvement occurred not later than a week after the termination of treatment. The duration of the improvement was highly variable, but the majority of the patients stated that they felt that the beneficial effect was somewhat decreasing after about two months. In six patients the relapse occurred in the course of 4—6 weeks. The majority of the patients were not subjected to further follow-up examinations, but three who have been admitted to the hospital for other diseases have remained symptom-free for from 6 months to 3 years.

Although, in most cases, the benefit was only of a transitory character, it was gratefully received by the patients. Two patients in the group »considerably improved» were in a veritable status asthmaticus at the institution of treatment and obtained a badly-required 'breathing space'.

Owing to the transitory improvement, some of the patients applied for further treatment. Seven patients received two, two patients three, and one patient four courses of treatment at intervals varying from 2 to 12 months. In two patients no improvement was obtained by the second course; in the remaining eight renewed treatment gave essentially the same result as before, *i. e.* improvement or absence of attacks lasting for from 1 to 3 months.

Discussion

Thus, roentgen irradiation of the lungs resulted in either cessation or marked decrease in the frequency and intensity of asthmatic attacks in four-fifths of the subjects. The relief occurred in all cases shortly after the completion of treatment and lasted for 2 months or more.

Investigators have discussed the explanation of this effect. It has been assumed that it is due to »protein shock», and irradiation of other organs (for example, the spleen) has been attempted although with doubtful effects. A possible explanation is that it is a question of psychic suggestion, since asthma, particularly in children, is responsive to psychic influences. However, our patients were adult persons with severe intractable asthma, in many cases of long duration. Furthermore, the constancy of the onset and duration of the improvement seems to militate against a psychic explanation.

Undoubtedly, the effect is due to a direct influence on the bronchi. In its mode of action, it bears a striking similarity to the effect of roentgen radiation in other benign diseases, notably the palliative effect on itching in eczema. The two diseases, bronchial asthma and eczema, are without doubt related to each other and must be regarded as essentially allergic. The most reasonable explanation might therefore be that the roentgen rays produce a desensitization of the sensory nerves, in other words, that it is a question of a slight analgesic effect.

It remains an open question whether the dosage employed is optimal. After a previous series with larger doses, LEDDY and MAYTUM adopted a more effective »low-dosage roentgen therapy» in which they applied a dose of 250 r to one large anterior and one large posterior mediastinal field, *i. e.* a smaller dosage than the one used by us. These authors suggested that a still lower dosage should be used. A comparison with the effect obtained in eczemas, in which small doses (100 r once or twice) may be beneficial, shows that it can scarcely be doubted that smaller doses may be sufficient in the majority of cases. Accordingly, we intend to halve the dosage in future. However, judging from our experience in the palliative effect on itching in eczemas, we believe that a dosage lower than one half will scarcely be fully adequate.

LEDDY and MAYTUM expressed the view that the best effect was obtained in severe long-standing cases in middle-aged persons. From the experience gained in the treatment of their series, they were at a loss to explain why the method of treatment failed in about 15 per cent of the cases. A study of the clinical features and laboratory findings (eosinophilia, etc.) did not lead to a classification of the cases which remained unaffected by roentgen therapy.

We have never been able to demonstrate any favorable effect on the frequently concurrent chronic bronchitis, which persists unchanged in spite of the reduction or cessation of the asthmatic attacks. In this connection it may be mentioned that we have attempted roentgen therapy in intractable chronic bronchitis without associated asthma, but without success.

A single course of treatment hardly involves any danger of radiation damage. In case of repetition caution should obviously be exerted. The method should scarcely be used in children; the tissues are more susceptible and the possibilities of late irradiation injuries cannot be excluded. Furthermore, roentgen treatment should not be instituted until all other therapeutic means, including attempts at elimination of any etiological factor, have been given a trial. For these reasons, the roentgen treatment of bronchial asthma ought to be reserved for middle-aged patients with long-standing chronic asthma.

SUMMARY

Roentgen treatment of the thorax in 48 patients with bronchial asthma resulted in a reduction or complete cessation of asthmatic attacks in 40 cases. In most cases the relief lasted about two months, in some instances longer. This method of treatment is recommended as a palliative in middle-aged and elderly patients with asthma of long standing.

ZUSAMMENFASSUNG

48 Patienten mit Asthma bronchiale erhielten Röntgenbehandlung des Thorax; bei 40 Patienten führte diese zur Abnahme oder zum völligen Verschwinden der Anfälle. Die Dauer der Verbesserung betrug in den meisten Fällen etwa 2 Monate, bei einigen Patienten hielt sie längere Zeit an. Die Röntgenbehandlung wird als palliative Methode für Patienten im mittleren und höheren Lebensalter mit langjährigen Asthmaleiden empfohlen.

RÉSUMÉ

La roentgenthérapie du thorax chez 48 malades, atteints d'asthme bronchique, a donné une réduction ou cessation complète des crises d'asthme dans 40 cas. Dans la plupart des cas le répit fut de deux mois environ, parfois plus. Cette méthode est recommandée comme palliatif chez les malades d'âge moyen ou vieux, asthmatiques depuis de nombreuses années.

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FROM THE ROENTGEN CLINIC (DIRECTOR: ERIK DE FINE LICHT), COPENHAGEN COUNTY HOSPITAL, GENTOFTE, DENMARK

CONCOMITANT ARTERIO-MESENTERIC OBSTRUCTION OF THE DUODENUM AND CHRONIC OESOPHAGITIS

Case Report

by

Erling Ratjen

The following is the case record of a 36-year-old woman with mega-duodenum and peptic oesophagitis. The combination of these recognised conditions is rare and a similar case record does not appear to have been previously published.

Mentally and physically normal up to the age of 16, she gradually developed the following symptoms:

After meals she had borborygmi and a sensation of oppression and of swelling in the epigastrium; relief was afforded a few hours later by vomiting; in addition there was pain in the epigastrium. The condition varied but during severe spells she vomited after every meal, suffered great loss of weight, and became exhausted and unfit for work.

During the previous 5 years, deglutition had been associated with pain in the cardiac region radiating to the back; the previous 12 months she could take only liquid or soft foods and had a feeling that its passage was obstructed at the level of the lower part of the sternum; on occasions she vomited mucus.

During the previous 20 years she had been in hospital with digestive disorders and intercurrent diseases: hepatitis, 9 years previously; nephritis and rheumatoid polyarthritis, 4 years later.

The symptoms of dyspepsia were associated with a number of others suggesting some hormonal disorder of unknown pathogenesis and stamped by a certain psycholability. The haemoglobin values, the standard metabolism and serum protein percentage often showed low figures.

Married for 5 years but had no children, she considered herself to be psychically normal; in 1950 she attempted suicide but for reasons unconnected with her disease.

A roentgen examination of the alimentary tract, carried out 14 years previously, had proved negative.

Condition on admission (January, 1951): The patient was in a miserable condition: weight 30 kilos. She was almost unable to swallow and a duodenal tube was passed

Submitted for publication Oct. 31, 1951.

down the oesophagus only with difficulty. During the period that followed, the patient's condition improved somewhat and roentgen examinations gave the following results:

Oesophagus: There was a stricture of the lower third with slight dilatation above; no definite demarcation line between these two areas. (On oesophagoscopy, the wall conveyed the impression of being rigid.) At the first examinations, the mucosal pattern was practically absent, later a coarse delineation of the mucous membrane appeared (Fig. 1). On one occasion a diaphragmatic hernia, the size of a walnut, was noted. There was never sign of ulceration.

The stomach and duodenum showed evidence of marked dilatation, the duodenal cap being particularly large; there was stasis as far as the duodeno-jejunal flexure, and the mucosal pattern was prominent. The position of the duodenum, duodenal flexure, small intestine and colon was normal. On one occasion contrast medium was injected into the duodenum through a duodenal tube (Fig. 2), the tip of which was then withdrawn to the stomach: during the next hour vigorous peristalsis with reflux to the stomach was observed in the duodenum, whereas nothing passed on into the jejunum. Only when the patient was placed on her left side did the contrast medium pass into the jejunum, the mucosa and size of which appeared to be quite normal.

The examinations suggested a condition of megaduodenum caused by an obstruction at the jejuno-duodenal flexure, caused by a peritoneal band or the superior mesenteric artery. It was thought that the changes in the oesophagus represented oesophagitis.

A review of the case suggests three possibilities:

(1) The megaduodenum was the primary lesion; the oesophagitis the secondary and caused by the peptic influence of the con'ents of the stomach.

(2) The small hiatal hernia with oesophagitis was the primary disorder, the megaduodenum being caused by constriction due to emaciation and asthenia.

(3) The condition was psychogenic and in the nature of nervous anorexia.

Laparotomy (O. KAPEL) was performed with the following findings:

»... After the colon had been everted it was seen that the superior mesenteric vessels were enclosed in a thick peritoneal induration which was firmly attached to the duodeno-jejunal flexure. The pancreas was normal. The subdiaphragmatic region was palpated, but nothing abnormal found ...« A very large and freely movable pars horisontalis duodeni was isolated. As the vomiting was severe, so much weight had been lost and an obstruction had been found, an isoperistaltic duodeno-jejunostomy was performed. The peritoneal fold found was believed to be the possible explanation of the obstruction.

After operation the patient's condition improved still further. Two months increased the weight by 4 kilos, and the vomiting which she had had for 20 years, ceased. She was able to swallow fairly well if she masticated her food thoroughly. The condition of the oesophagus improved somewhat but the roentgenologic findings remained fundamentally unchanged.

If abnormal congenital conditions of the intestine are left out of consideration, the most probable causes of obstruction at the duodenal flexure are: Atresia or intestinal webs (ERNST, DAHL-IVERSEN, BRATTSTRÖM, HUBLIN), or compression by a peritoneal band or the superior mesenteric artery (PETRÉN, CHAMBELL, WAHREN). It has been maintained by several authors (PETRÉN, NORDENTOFT) that a mechanical explanation of a megaduodenum cannot always be found; MELCHIOR in 1924 introduced the conception of the idiopathic megaduodenum,

Fig. 1. Fig. 2.

Fig. 1. Stricture of the distal third of the oesophagus. Fig. 2. Pronounced ectasy of the duodenum. Distinct stasis at the jejunal flexure.

and KOSTLIVY suggested a neuromuscular disturbance as an explanation of chronic infra-papillary stenosis in his cases. It is stated that the disorder is of most frequent occurrence in neurotic individuals but the frequency of neurosis and thus the possibility of coincidence should be borne in mind. Moreover, the prolonged disease may produce psychic changes; the patient's relatives may often be instrumental in this by labelling the patient as neurotic in the absence of any other explanation. HILLEMAND and DUGUÉ have reported two cases of megaduodenum in patients with nervous anorexia; these undoubtedly lend themselves to the same »post and propter hoc» arguments.

Finally, extreme emaciation may favour ptosis of the duodenum with possible kinking at the flexure and constriction by the superior mesenteric artery.

The conditions for the development of oesophagitis are present when the acid stomach contents come into frequent contact with the oesophageal mucous membrane. The constant vomiting may have been

the cause of the roentgenologic changes which correspond to WELIN and BERGQUIST's 2nd (fulminating) and 3rd (stenosing) stages.

ALLISON (1948) has pointed out that oesophagitis is most frequently associated with and developed as a consequence of a hiatal hernia; only 2 in a series of 63 cases had no hernia.

THOMSEN (1949) found no hernia in 9 out of 16 adult patients with peptic oesophageal ulceration. Hiatal hernia was not found in any of WELIN's or LÜDIN's patients with oesophagitis.

JACKSON found a heterotopic mucous membrane of the stomach in 8 per cent of cases with oesophagitis; we do not know whether this played any part in our case.

Whether an ulcer crater is found or not in oesophagitis, does not affect the diagnosis (ALLISON, STEINER); the ulcer may have healed when the patient is examined.

The situation of the inlet of the oesophagus at the superior aspect of the hernia is in accordance with the general configuration of a congenital hernia. HARRINGTON has described a type of oesophageal hiatus hernia (the »pulsion type»). Here the oesophagus enters a small protruded cardiac portion of the stomach above the diaphragm. In case of a complicating oesophagitis the hernia may be held elevated above the dome by cicatrization in and around the shortened oesophagus. Any distinction between congenital and acquired hernia at this stage of the disease is impossible (SHANKS & KERLEY).

Daily vomiting over years offers a sufficient explanation for the development of a hiatal hernia. Assuming the case in question to be one of congenital hernia it seems strange that symptoms did not appear until the 16th year of life.

The size of the diaphragmatic hiatus was not obvious from subdiaphragmatic palpation. The small size of the hiatal hernia probably contributed to the difficulty in confirming the roentgenologic findings.

Some improvement in the condition of our patient has taken place and the vomiting has ceased. On the other hand it is improbable that a complete cure of the oesophagitis will be effected; the changes are advanced ones and there is still regurgitation through the cardia. The treatment has, however, improved her physical and mental condition to such an extent that a surgical operation on the thorax may be considered if necessary.

SUMMARY

The author describes and discusses a case in whom roentgen examinations revealed a megaduodenum with obstruction at the duodeno-jejunal flexure, stenosing oesophagitis and a small hiatal hernia. A peritoneal fold containing the superior mesenteric artery and attached to the duodenal flexure was found at operation.

ZUSAMMENFASSUNG

Der Verf. beschreibt und diskutiert einen Fall, bei welchem die Röntgenuntersuchungen ein Megaduodenum mit Obstruktion an der Flexura duodeno-jejunalis, eine stenosierende Ösophagitis und eine kleine Hiatushernie aufzeigten. Bei der Operation fand man eine Peritonealfalte, welche die Arteria mesenterica sup. enthielt und mit der Flexura duodeno-jejunalis verbunden war.

RÉSUMÉ

L'auteur décrit et discute un cas dans lequel l'exploration radiologique a révélé un mégaduodénum avec obstruction au niveau de l'angle duodéno-jéjunal, oesophagite sténosant et petite hernie du hiatus diaphragmatique. Lors de l'opération on découvrit un repli péritonéal, contenant l'artère mésentérique supérieure et adhérent à l'angle duodéno-jéjunal.

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DIE 31-MeV-BETATRONANLAGE DER RADIOTHERAPEUTISCHEN KLINIK IM KANTONSSPITAL ZÜRICH

von

H. R. Schinz und *R. Wideröe*

Die 31-MeV-Betatronanlage der radiotherapeutischen Klinik im Kantonsspital der Universität Zürich dient in erster Linie zur Herstellung ultraharter Röntgenstrahlen und wird seit April 1951 für den regulären Therapiebetrieb benützt. Sie ist die erste Betatronanlage für Tiefentherapie auf dem europäischen Kontinent.

Das von der Firma *Brown Boveri, Baden*, Schweiz, entwickelte 31-MeV-Betatron weist verschiedene bemerkenswerte Eigenschaften auf und unterscheidet sich in vieler Hinsicht von den bisher gebauten ähnlichen Maschinen. Im folgenden soll eine kurze Beschreibung der Anlage, sowie einiges über die Eigenschaften der erzeugten ultraharten Röntgenstrahlen gebracht werden.

1. Die Betatronanlage

Das Prinzip der Elektronenbeschleunigung im Betatron darf als bekannt vorausgesetzt werden und sei deswegen hier nur kurz erwähnt. Wie die auch vielfach gebrauchte Bezeichnung »Strahlentransformator« ausdrückt, hat die Wirkungsweise der Maschine grosse Ähnlichkeit mit jener eines gewöhnlichen Transformators. Mit Hilfe einer Niederspannungswicklung wird ein magnetischer Wechselfluss erzeugt. Um diesen Wechselfluss werden Elektronen durch magnetische Führungsfelder gesteuert und zu einer Kreisbewegung mit sehr vielen Umläufen gebracht. Die in einer Vakuumröhre kreisenden Elektronen, die gewissermassen mit der Hochspannungswicklung des gewöhnlichen Transformators zu vergleichen wären, gewinnen bei jedem Umlauf eine Energie

Bei der Red. am 6. XI. 1951 eingegangen.

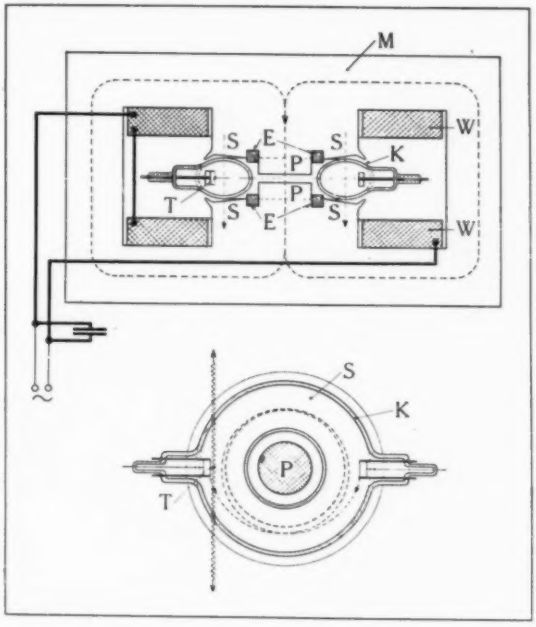

Abb. 1. Prinzipschema des Zürcher Betatrons von 31 MeV (Vertikaler und horizontaler Schnitt).

Zweistrahlbetrieb.

M = Eisenkörper des Magnetkreises,
P = Zentrale Magnetpole,
S = Steuerpole,
W = Erregerwicklungen,
E = Expansionswicklungen,
K = Kreisröhre,
T = Antikathode (»Target»).

entsprechend der Windungsspannung des Transformators, beispielsweise im Mittel 31 Volt. Da die Elektronen vermöge ihrer grossen Geschwindigkeit sehr viele, beispielsweise eine Million Umläufe während der Beschleunigungszeit ausführen können, werden sie am Ende eine sehr grosse Energie von vielen Millionen Volt, beispielsweise bei der Zürcher Maschine 31 Millionen Volt erreichen, wobei sie im Laufe von 1/200 Sekunde einen Weg von 1,500 km zurückgelegt haben. Die hochenergetischen Elektronen werden in einer Antikathode abgebremst und erzeugen dabei mit einem Wirkungsgrad von etwa 35 % eine ultraharte Röntgenstrahlung, deren kleinste Wellenlänge nur etwa 0.4 X Einheiten ($= 0.4 \cdot 10^{-3}$ Å) beträgt.

Abb. 1 zeigt die prinzipielle Wirkungsweise des 31-MeV-Strahlentransformators. Der Magnetkörper hat in der Mitte einen Luftspalt und am äusseren Rand speziell geformte Steuerpole für die Führung der Elektronen. Zwischen den Steuerpolen befindet sich die kreisförmige, aus Glas hergestellte Vakuumröhre. In diese Vakuumröhre sind zwei Elektronenspritzen eingebaut, mit deren Hilfe Elektronen tangential auf die Kreisbahn eingeführt werden können. Die Elektronenspritzen sind gegeneinander um 180° versetzt und werden abwechselnd nacheinander erregt. Je nach der Richtung des magnetischen Wechselfeldes kreisen

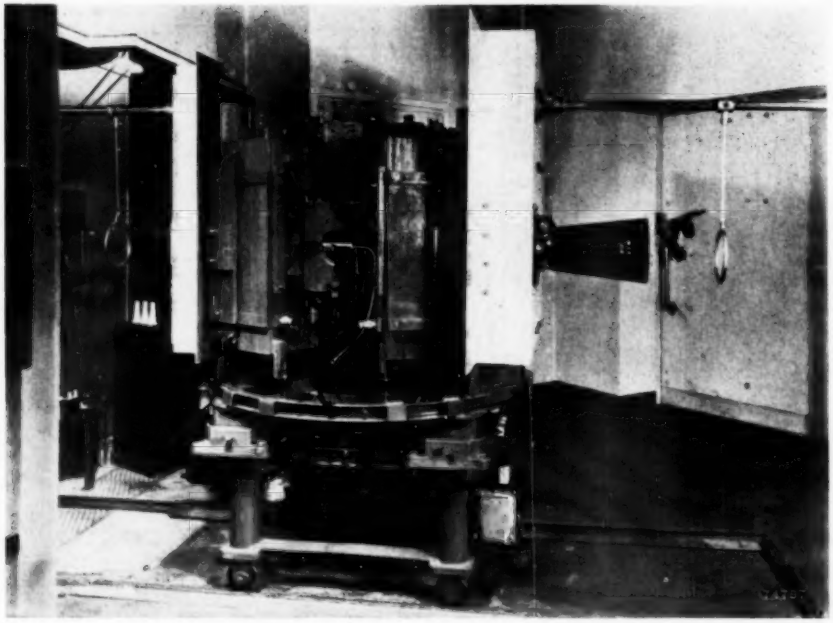

Abb. 2. Betatron mit Schutzwänden von der Seite gesehen. Rechts und links sind die Tubusse für die Bestrahlung der Patienten sowie die Visiereinrichtungen sichtbar.

somit die Elektronen im Uhrzeigersinn oder umgekehrt in der Röhre, und sie treffen die auf der einen Elektronenspritze angebrachte Antikathode abwechselnd von rechts oder von links. Wir erhalten somit intermittierend je einen nach rechts und nach links gerichteten Röntgenstrahl. Die Röntgenblitze, die in dieser Weise erzeugt werden, haben eine Dauer von ca. 10 μsek.; ihre Intensität ist aber so gross, dass für jeden Strahl eine mittlere Röntgenstrahlintensität von über 100 r/min. in 1 m Abstand (gemessen hinter Blei) erreicht werden kann. Abb. 2 zeigt den Strahlentransformator, während Abb. 3 die Disposition der Zürcher Anlage darstellt. Das Betatron befindet sich in einem schmalen Gang zwischen den beiden Bestrahlungsräumen hinter Eisenwänden, die mit Bleiplatten verkleidet sind. An diesen Gang anschliessend ist ein Maschinenraum angeordnet mit den notwendigen Einschaltgeräten für den Anschluss an das 380-V/50-Hz-Netz sowie die Kondensatorbatterien, welche den für die Maschine notwendigen Magnetisierungsstrom liefern. Der Energiebedarf der Anlage beträgt etwa 14 kW. Der allergrösste Teil dieser Energie wird in Verlustwärme umgewandelt und

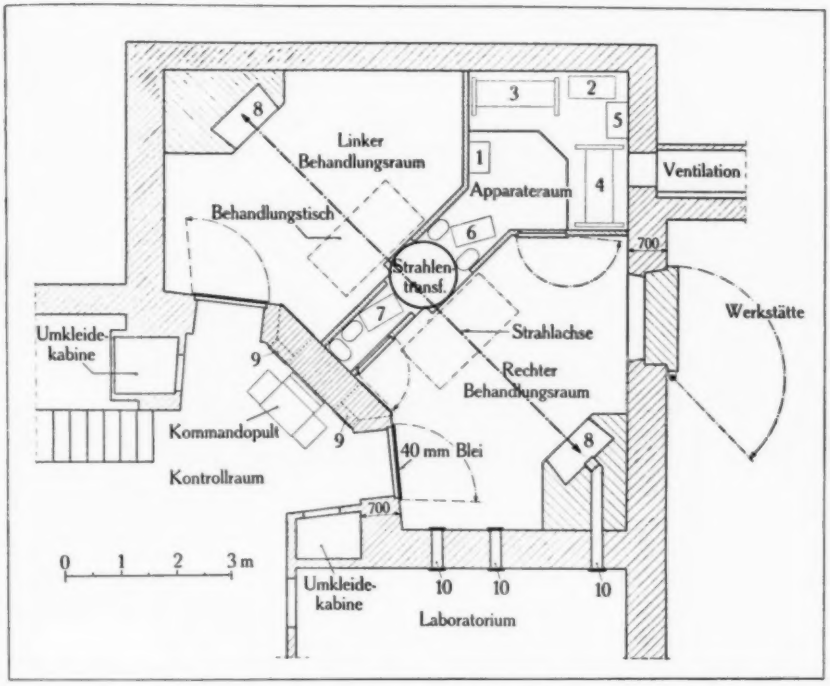

Abb. 3. Disposition der Betatronanlage im Kantonsspital Zürich.
1 = Schaltschrank für den Netzanschluss, 2 = Transformator 380/6,000 Volt, 3 und 4 = Kondensatorenbatterien, 5 = Expansionsapparatur, 6 und 7 = Impulsgeräte, 8 = Strahlenauffänger, 9 = Beobachtungsfenster, 10 = Messkanäle. Schraffiert = Wände aus mindestens 700 mm Beton.

mit der Kühlluft durch eine Ventilatoranlage entfernt. Die beiden Bestrahlungsräume, in welchen zwei Patienten ganz unabhängig voneinander gleichzeitig behandelt werden können, sind durch Bleiwände getrennt; das Bedienungspersonal kann sich deshalb eine angemessene Zeit in dem einen Raum aufhalten, während in dem anderen Raum bestrahlt wird.

Das Kontrollpult mit den Einstell- und Messgeräten für die beiden Strahlen befindet sich in einem angrenzenden Raum. Die Patienten können von hier aus durch eine Spiegeloptik während der Bestrahlung überwacht werden. Die Bestrahlungsräume werden durch 40 mm dicke Bleitüren vom Kontrollraum abgeschlossen, und die Schaltung der Anlage ist zum Schutz des Bedienungspersonals so eingerichtet, dass die Strahlerzeugung beim Öffnen der Türen unterbrochen wird. Die

Abb. 4. Lagerung eines Patienten bei Behandlung eines Oesophagus-Karzinoms.

Patienten sind, den festgelegten Strahlachsen entsprechend, in einer bestimmten Lage zu behandeln. Sie werden zu diesem Zwecke auf normalen, in der Höhe verstellbaren Behandlungstischen mit Gurten angeschnallt. Abb. 4 zeigt die Lagerung des Patienten bei Behandlung eines Speiseröhrenkarzinoms. Diese Methode, die anfänglich etwas problematisch schien, hat sich im Laufe der Zeit gut bewährt, und man kann sagen, dass die feste Lage der Strahlachse heute nur noch als unbedeutender Nachteil angesehen werden kann.

2. Eigenschaften der ultraharten Strahlung

Die ultraharte Strahlung unterscheidet sich in vieler Hinsicht von der gewöhnlichen 200-kV-Röntgenstrahlung. Die ultraharte Strahlung ist sehr stark in der Einfallsrichtung der Elektronen gebündelt. Bei 31 MeV beträgt die Halbwertbreite der Strahlung nur $\pm 3.3°$. Dies bringt grosse Vorteile für die Abschirmung der Strahlung mit sich, bereitet aber Schwierigkeiten, wenn eine gleichmässige Belichtung eines Feldes verlangt wird. Man kann eine Homogenisierung der Strahlenintensität durch Ausgleichkörper erreichen, die eine Herabsetzung der Strahlenintensität in der Strahlachse erzeugen. Abb. 5 zeigt die Anordnung des aus einer Kupfermischung hergestellten Ausgleichkörpers in der 31-MeV-Maschine. Der konische Ausgleichkörper ist ganz vorne, möglichst dicht an der Kreisröhre, angebracht. Dies hat den Vorteil,

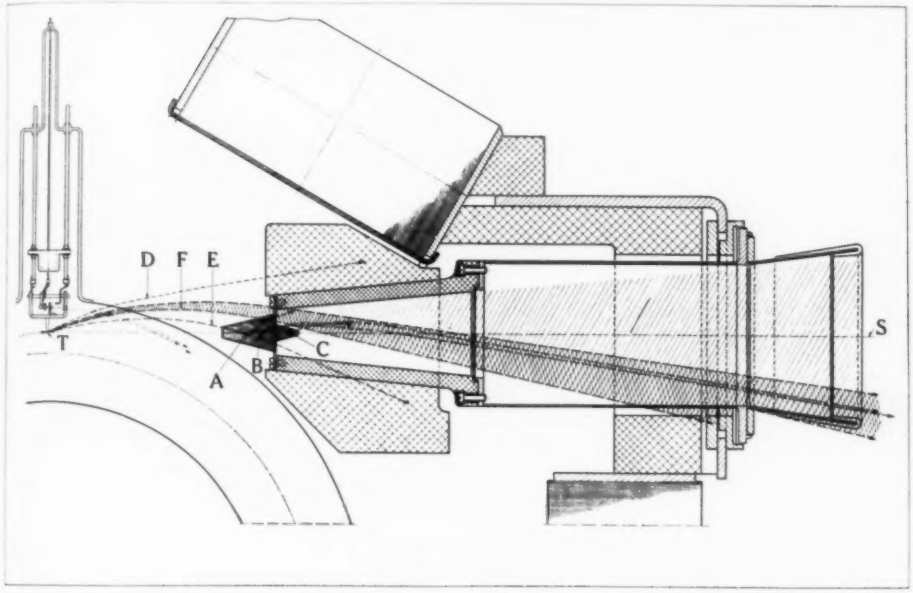

Abb. 5. Schnitt durch den Strahlentransformator in der Kreisbahnebene. Blenden verhindern den Eintritt der Elektronen in das Röntgenstrahlfeld.
T = Antikathode (»Target«), T—S = Strahlachse, D, E, F = Bahnkurven von 10-MeV-Elektronen, die durch die Antikathode hindurchgegangen sind. Nur die F-Elektronen können durch die Blende hindurchgelangen. A, B, C = Bahnkurven von Comptonelektronen, die Energien von 3.2 und 1 MeV haben und im konischen Ausgleichkörper durch die Röntgenstrahlung erzeugt werden.

dass die im Ausgleichkörper erzeugten Comptonelektronen durch das magnetische Streufeld abgelenkt werden und praktisch nicht in den Strahlengang der Röntgenstrahlung gelangen können. Sekundärelektronen haben eine relativ kurze Reichweite im Gewebe und könnten die Werte der Tiefendosen der Strahlung sehr ungünstig beeinflussen. Aus dem gleichen Grunde müssen auch die aus einer nichtleitenden Bleimischung hergestellten Röntgenblenden möglichst nahe an der Kreisröhre angebracht werden. In der Abb. 5 sind noch Bahnkurven von Elektronen eingezeichnet, die nicht in der Antikathode vollständig abgebremst werden und durch die Glaswände der Kreisröhre ins Freie austreten. Auch solche Elektronen können bei zweckmässiger Anordnung der Blenden weitgehend vernichtet werden. Abb. 6 zeigt Tiefendosiskurven. Wie man daraus ersieht, erreichen wir mit der von Elektronen gesäuberten 31-MeV-Strahlung eine Tiefendosis in 10 cm Wassertiefe von ca.

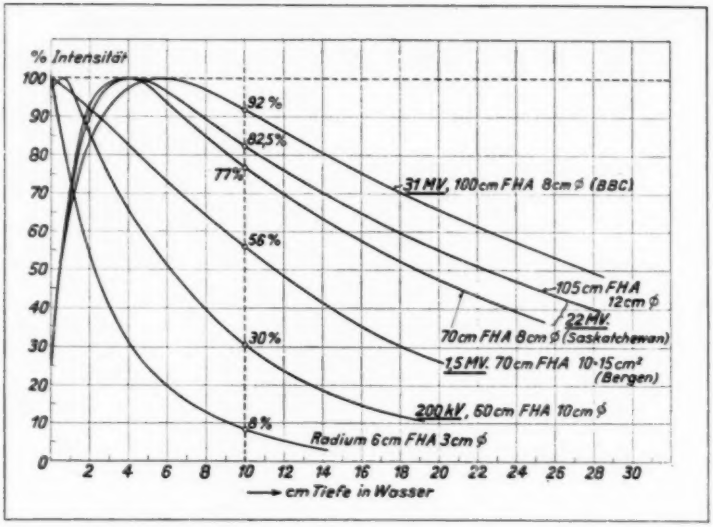

Abb. 6. Tiefendosiskurven der Röntgenintensität in Wasser für verschiedene Elektronenenergien.

Abszisse = Tiefe in Wasser (cm), Ordinate = Intensität (%), FHA = Fokus-Haut-Abstand, 8 cm ⌀ = Röntgenfeld an der Hautoberfläche von 8 cm Durchmesser usw. Aus den Kurven geht hervor, wie die Tiefendosis bei steigender Strahlenergie immer höhere Werte erreicht, während die Eintrittsintensität an der Haut gering bleibt.

92 % des Maximalwertes von 100 % in 6 cm Wassertiefe. Die Eintrittsdosis ist klein, nur etwa 25 %, während die Intensität an der Austrittsstelle Werte von über 60 % annimmt. Eine Erhöhung der Strahlenenergie über 31 MeV hinaus würde die Tiefendosis in 10 cm Wassertiefe noch weiter gegen 100 % erhöhen können, aber die Austrittsdosis würde ebenfalls ansteigen und somit die Verhältnisse ungünstiger gestalten. Gleichzeitig würde auch die im Körper verabreichte Volumendosis erhöht werden. Abb. 7 zeigt die Volumendosis bei der Betatronstrahlung, verglichen mit jener bei 200-kV-Röntgenstrahlung. Man könnte geneigt sein, zu glauben, dass die ultraharte Strahlung wegen des langsamen Intensitätsabfalls in der Tiefe hinsichtlich der Volumendosis viel ungünstigere Verhältnisse als die der 200-kV-Strahlung ergeben müsste. Wie man nun aber aus Abb. 7 ersieht, sind diese Verhältnisse weitgehend von der Dicke des durchstrahlten Körpers sowie von der Tiefe des zu behandelnden Krebses abhängig. Bei geringer Tiefe des Krebsherdes und grosser Dicke des durchstrahlten Körpers wird die Betatronstrahlung tatsächlich auch eine grössere Volumendosis als die 200-kV-Strahlung

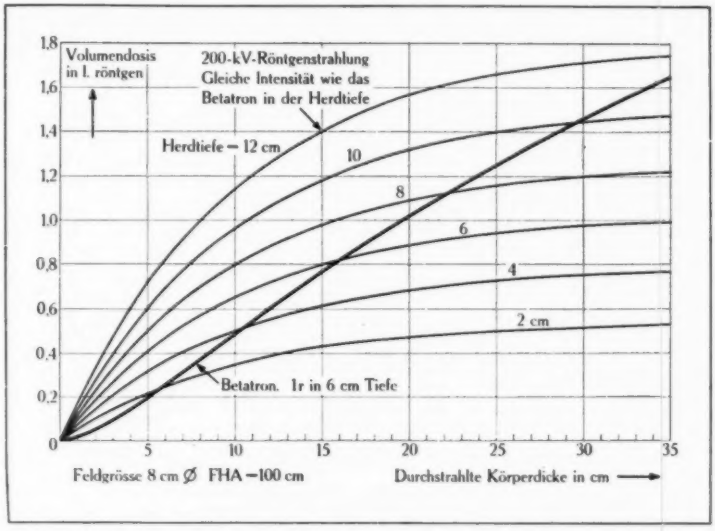

Abb. 7. Vergleich zwischen der in einem Körper erzeugten Volumendosis bei 200 kV und bei 31 MeV Betatronstrahlung. Die für das Betatron gültige Kurve gibt die Volumendosis in Liter-röntgen für verschiedene durchstrahlte Körperdicken an, unter der Voraussetzung, dass die Dosis in 6 cm Tiefe 1 röntgen beträgt.

1 l röntgen = 1 Liter-röntgen = die Volumendosis in 1 Liter Wasser bei 1 r mittlerer Intensität. Die Kurven für die 200-kV-Röntgenstrahlung sind unter der Voraussetzung berechnet worden, dass die Intensität der Strahlung in 2, 4, 6, 8, 10 und 12 cm Tiefe die gleiche wie bei der Betatronbestrahlung ist. Für die 200-kV-Strahlung wurde eine Tiefendosis (in 10 cm Tiefe) von ca. 30 % angenommen.

erzeugen. Hingegen sind bei den tieferliegenden Krebsen, deren Behandlung vor allem zum Begriff »Tiefentherapie» geführt hat, die Verhältnisse meistens für die ultraharte Strahlung günstiger als für die 200-kV-Strahlung. Man kann aus dem Kurvenblatt Abb. 8 leicht jene Fälle abgrenzen, die sich für eine Behandlung mit der Betatronstrahlung besonders eignen.

Zu der Bestrahlungstechnik sei noch erwähnt, dass eine Reihe von Blenden mit entsprechenden Ausgleichkörpern verwendet werden, mit denen man die praktisch gewünschten Bestrahlungsfelder einstellen kann. Wie Abb. 9 zeigt, ist die Definition des Röntgenfeldes ausserordentlich scharf, und diese Schärfe der bestrahlten Fläche bleibt auch in der Tiefe des Körpers bestehen. Ausserhalb des bestrahlten Feldes ist die Intensität sehr gering, im Mittel kleiner als 1 ‰, sodass eine nennenswerte Erhöhung der verabreichten Volumendosis vermieden wird.

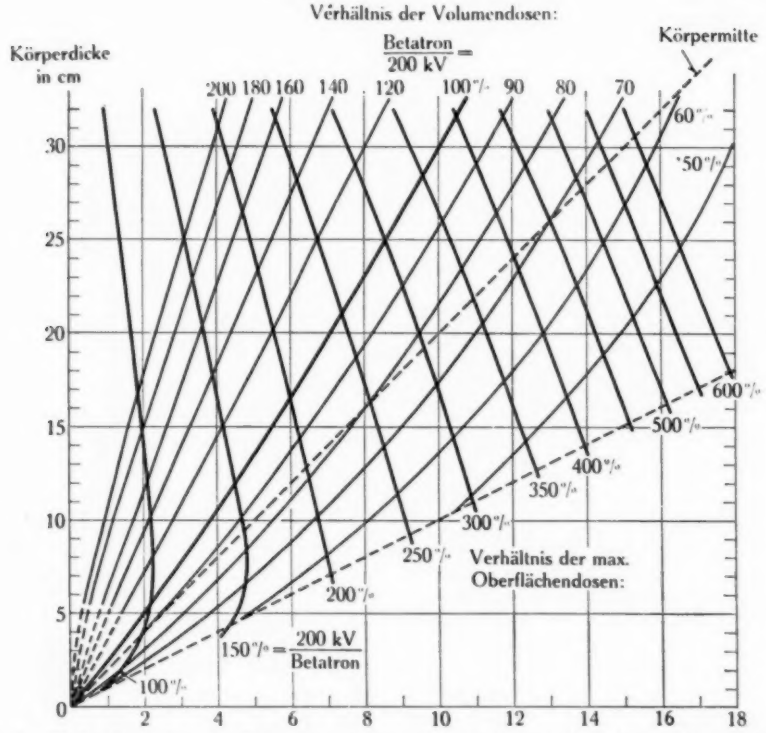
Verhältnis der Volumendosen:
Körperdicke in cm
Betatron / 200 kV =
Körpermitte
200 180 160 140 120 100 % 90 80 70 60 % 50 %
600 %
500 %
400 %
350 %
300 %
250 %
200 %
150 % = 200 kV / Betatron
100 %
Verhältnis der max. Oberflächendosen:
0 5 10 15 20 25 30
2 4 6 8 10 12 14 16 18

Abb. 8. Tiefentherapie mit Röntgenstrahlen. Vergleich zwischen der bisher üblichen 200-keV-Strahlung einer normalen Röntgenanlage und jener des 31-MeV-Strahlentransformators (Betatron) bei gleicher Röntgendosis am Krankheitsherd.

Abszisse = Tiefe des zu bestrahlenden Krankheitsherdes (Herdtiefe) in cm, Ordinate = durchstrahlte Körpertiefe in cm. A = Körpermitte, B = Verhältnis der Volumendosen, C = Verhältnis der maximalen Oberflächendosen.

Die Schutzmassnahmen für das Bedienungspersonal haben sich gut bewährt; die Intensität im Kontrollraum liegt im Mittel unterhalb 3 mr/h und erreicht nur an wenigen Stellen, z. B. ganz in der Nähe der Türspalten, den Wert der Toleranzdosis von 6.2 mr/h.

Die Dosimetrierung der Strahlung wird mit bleigeschützten Ionisationskammern ausgeführt, die von einer seitlich dem Bestrahlungsfeld verlaufenden Nebenstrahlung durchsetzt werden. Der in diesen Ionisationskammern fliessende Strom wird verstärkt und gemessen. Diese Messeinrichtungen werden in regelmässigen Zeitabständen mittels Victoreen-Fingerhutkammern, die in ein von der Hauptstrahlung durch-

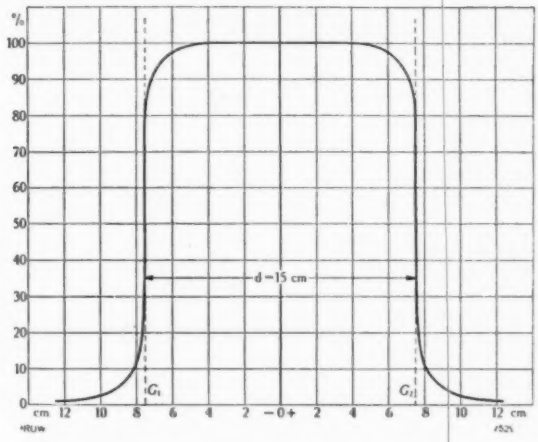

Abb. 9. 31-MeV-Röntgenstrahlintensität in Luft, senkrecht zur Strahlachse gemessen. Die Messung erfolgte durch Photometrieren eines mit Röntgenstrahlen belichteten Films. Die Kurve gibt Mittelwerte der Messpunkte an. Durchmesser des Strahlenfeldes = 15 cm in 75 cm Abstand von der Antikathode.

setztes Plexiglasphantom eingebettet sind, geeicht und kontrolliert. Auf diese Weise lässt sich die Tiefendosis mit einer hinreichenden Genauigkeit — die Abweichungen dürften nur wenige Prozente betragen — messen. Die im Kontrollraum vorhandene Strahlenintensität wurde mit einem amerikanischen »Radiation survey meter» gemessen; dieses Gerät enthält eine Ionisationskammer mit eingebautem Gleichstromverstärker.

3. Klinische Erfahrungen

Die verhältnismässig kurze Betriebszeit der Betatronanlage von nur sieben Monaten erlaubt natürlich noch kein abschliessendes Urteil über die Eignung der ultraharten Strahlung für die *Behandlung tiefliegender Krebse*. Der zu erwartende Hauptvorteil der Betatronstrahlung liegt zweifelsohne in der überaus günstigen Tiefendosiskurve mit der geringen Hautbelastung und in der durch den ganzen Körper verlaufenden scharfen Strahlbegrenzung. Diese Vorteile gegenüber der bisherigen 200-kV-Strahlung haben sich bereits praktisch bewährt. Bei den bisher behandelten über 60 Patienten waren die Hautreaktionen an der Eintrittsstelle der Strahlung nur sehr schwach. An der Austrittsstelle der Strahlung trat bei Gesamtdosen von über 4,000 bis 12,000 r je nach Körperdicke in der Regel eine leichte Hautrötung auf, die aber bald wieder zurückging und zu keinen Komplikationen führte. Eine eigentliche Radioepidermitis exsudativa trat nie auf.

Mit Ausnahme von wenigen besonders sensiblen Patienten vertrug die Mehrzahl derselben die Betatronbehandlung gut. Unerwünschte Nebenerscheinungen, wie Schwächegefühl, Übelkeit, Schwindel und

Erbrechen sind im allgemeinen geringer als bei der gewöhnlichen Röntgenbestrahlung, obwohl in einzelnen Fällen Gesamtdosen von bis über 12,000 r (Tiefendosis in 6 cm Tiefe) verabreicht wurden, wobei anfänglich die täglich verabreichte Einzeldosis 240 r betrug. Später wurde die Einzeldosis auf 300 r erhöht. Weitere Erhöhungen der Einzeldosis können je nach Indikation jederzeit vorgenommen werden. Die Reaktion des Krebsgewebes auf die ultraharte Strahlung scheint im Prinzip gleich zu verlaufen wie bei der bisherigen 200-kV-Strahlung. Im allgemeinen können wir die bereits in Amerika gemachten Erfahrungen bestätigen, dass die biologische Wirksamkeit der ultraharten Strahlung bei gleicher Ionenzahl etwas geringer ist als bei der 200-kV-Strahlung. Wir rechnen heute vorläufig mit einem biologischen Faktor von etwa 0.65—0.70 für die Betatronstrahlung. Das statistische Material ist jedoch noch zu gering, um sichere Schlüsse zu ziehen. Die ungleiche biologische Wirksamkeit, die übrigens bei verschiedenen Geweben des gleichen Objektes und bei verschiedenen Lebewesen ganz verschieden sein kann (auf Bakterien scheint die ultraharte Strahlung stärker einzuwirken), hängt wahrscheinlich mit der Verteilungsdichte der von der ultraharten Strahlung gebildeten Ionen zusammen. Sicher bewirkt die ultraharte Strahlung eine gleichmässigere Ionenverteilung als die 200-kV-Strahlung. Es scheint deshalb nicht ausgeschlossen, dass die ultraharte Strahlung im biologischen Objekt gegenüber der 200-kV-Strahlung spezifische Unterschiede aufweisen kann, die für die Therapie von Bedeutung sein können. Um diese Verhältnisse zu klären, müssen noch viele strahlenbiologische Versuche ausgeführt werden. Die Frühresultate bei Krebsen sind günstig. Wir haben sie für 44 Fälle zusammengestellt. Es handelt sich dabei um Krebse der verschiedensten Lokalisation. Die angewendeten Dosen sind sehr verschieden. Wir müssen hier noch weitere Erfahrungen sammeln. Immerhin möchten wir feststellen, dass wir bei 7 Krebsen des Pharynx und des Larynx eine Symptomfreiheit erzielt haben, währenddem wir bei einem Krebs der Zungenbasis mit einer wegen des schlechten Allgemeinzustandes nur niedrigen Dosis nur eine Besserung erzielten. Auch die Früherfolge bei Speiseröhrenkrebsen sind besser als früher. Noch nicht zufrieden sind wir bei den Bronchialkarzinomen, müssen aber darauf hinweisen, dass die Frühfälle heute alle operiert werden und dass wir nur sehr späte Stadien zur Behandlung bekommen. Weitere Einzelheiten gehen aus der Tabelle s. 385 hervor. Wir glauben aber, auf einem guten Wege zu sein.

Die Betatronanlage in Zürich dient ausser dem regulären Therapiebetrieb auch in hohem Masse der *strahlenbiologischen Forschung;* diese ist Voraussetzung der Strahlentherapie. Ohne strahlenbiologische Forschung gibt es keine Fortschritte in der Krebstherapie. Bis jetzt sind in grossen Zahlen Bestrahlungen von Drosophilaeiern und von Droso-

Betatronbestrahlung bei Malignomen (44 Fälle)

Krankheitsgruppen	Zahl der Fälle	Dosis in r in 5,3 cm Tiefe (Victoreen)	Symptomfrei	Gebessert	Unbeeinflusst
Carcinome der oberen Luft- und Speisewege					
Epipharynx	1	6,000—9,000	1		
Mesopharynx	1		1		
Hypopharynx	2		2		
Innerer Larynx	2		2		
Äusserer Larynx	1		1		
Zungenbasis	1	4,000		1	
Oesophagus-Carcinome	7	10,000—13,000	3	3	1
Bronchial-Carcinome	9	5,000—9,000		4	5
Rectum-Carcinome	1	12,000	1		
Genital-Carcinome					
Ovar	1	4,000—9,000	1		
Corpus uteri	2		2		
Cervix	1			1	
Portio	6		3	2	1
Vagina	1		1		
Metastasen					
Lymphogranulomatose	4	3,000—7,000	4		
Lymphosarkom	1	4,000	1		
Grossfollikul. Lymphoblastom	1	5,000	1		
Struma maligna	1	7,200		1	
Chorionepitheliom	1	8,000		1	

philapuppen durchgeführt worden in Form eines Letalitätstestes, eines Modifikationstestes und eines Mutationstestes. Ein beliebtes Forschungsobjekt sind für uns auch Froscheier. Über die strahlenbiologischen Ergebnisse wird an anderer Stelle berichtet.

4. Weitere Anwendungsbereiche

Ausser zu therapeutischen und strahlenbiologischen Zwecken wird das Betatron auch weitgehend für *kernphysikalische* Untersuchungen, besonders für photonukleäre Prozesse benützt. Abb. 10 zeigt die durch die ultraharte Strahlung erzeugte Explosion eines Kohlenstoffkernes. Dieser zerfällt in drei Alphateilchen, d. h. in drei Heliumkerne. Aus der Reichweite der Kerntrümmer lässt sich die Energie der Röntgenstrahlung — sie betrug in diesem Falle 30.4 MeV — ermitteln. Die Erzeugung von radioaktiven Isotopen mit den Kernreaktionen der

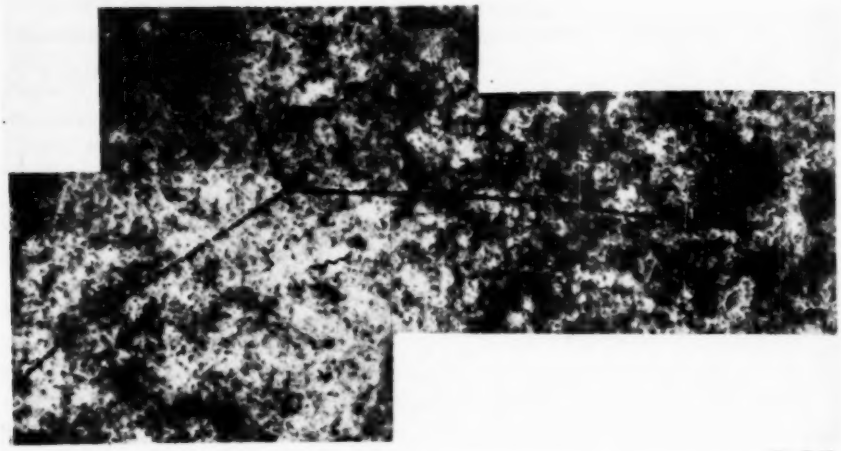

Abb. 10. Mikrophotographie eines durch ein 30.4-MeV-Quant zur Explosion gebrachten Kohlenstoffkernes. Vergrösserung 1,700fach. Die drei auseinandergeschleuderten α-Teilchen (Heliumkerne) haben eine Energie von 23.1 MeV.

Betatronstrahlung eröffnet ein neues Feld, dessen Bedeutung noch nicht zu übersehen ist. Es scheint aus bisherigen Vorversuchen erwiesen, dass man radioaktive Isotopen in solchen Mengen herstellen kann, dass sie für Tracer-Versuche ausreichen. Dagegen dürften die auf diese Weise erzeugten Isotopen für eine Isotopentherapie wohl kaum genügen.

Um die vielseitige Anwendbarkeit der Betatronanlage in Zürich noch weiter zu beleuchten, sei schliesslich erwähnt, dass das Betatron auch häufig für technische Materialuntersuchungen (Grobstrukturuntersuchungen) verwendet wird. Die Durchleuchtung von dicken Eisenplatten, von Schweissnähten und von Gusskörpern gelingt mit der ultraharten Strahlung in einem Bruchteil der bisher angewendeten Zeiten und ermöglicht auch bei ganz dicken Eisenteilen eine sonst unerreichbare Fehlererkennbarkeit. Beispielsweise sei erwähnt, dass man in einer 300 mm dicken Eisenplatte kleine Löcher von weniger als 1.4 mm Durchmesser noch gut erkennen kann, und dass Haarrisse von nur 0.05 mm Breite noch deutlich sichtbar sind.

Über weitere Resultate mit dem Betatron in Zürich werden sowohl die Physiker der Universität wie der Eidgenössischen Technischen Hochschule in Zürich Bericht erstatten, ebenso der Physiker der radiotherapeutischen Klinik in Zürich (P. D. Dr. Joyet), die Leiterin des strahlenbiologischen Laboratoriums (P. D. Dr. Fritz-Niggli) und mein Stellvertreter (P. D. Dr. K. Hohl) mit den Assistenten der radiotherapeutischen Klinik.

ZUSAMMENFASSUNG

Seit April 1951 wird in der radiotherapeutischen Klinik im Kantonsspital der Universität Zürich eine 31-MeV-Betatronanlage für den regulären Röntgen-Therapiebetrieb verwendet.

Der Aufsatz enthält eine kurze Beschreibung der von der Firma Brown-Boveri, Baden (Schweiz) entwickelten Betatronanlage sowie einiges über die Eigenschaften der ultraharten Röntgenstrahlung und die mit ihnen bis jetzt erzielten klinischen Frühresultate.

SUMMARY

A 31 MeV betatron installation belonging to the Radiologic Institute of Zurich University has been in service for regular roentgen therapy at the Radiotherapeutic Clinic of the Zurich Cantonal Hospital since April, 1951.

The authors briefly describe the betatron installation developed by Brown, Boveri & Co. Ltd., Baden, Switzerland, discuss certain properties of ultra-hard roentgen radiation, and finally give some preliminary clinical results obtained with the installation at Zurich.

RÉSUMÉ

Un bétatron de 31 MeV appartenant à l'Institut de Radiologie de l'Université de Zurich est en service depuis le mois d'avril 1951 à la Clinique de Radiothérapie de l'Hôpital Cantonal de Zurich.

L'article contient une brève description de ce bétatron étudié et construit par la Société Anonyme Brown, Boveri & Cie à Baden, Suisse, ainsi que quelques indications sur les propriétés de son rayonnement ultra-pénétrant et sur les résultats thérapeutiques obtenus jusqu'ici.

FROM THE INSTITUTE OF RADIOPHYSICS OF THE KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM, SWEDEN (DIRECTOR: PROF. ROLF M. SIEVERT)

VARIATIONS IN NATURAL γ-RADIATION IN SWEDEN

by

Rolf M. Sievert and *B. Hultqvist*

Radiation hazards in the modern community form a continuously increasing factor which will probably become an important social question in the near future. For this reason, it may be of some interest to know the natural irradiation conditions under which mankind is living, irrespective of the use of penetrating radiations in scientific and practical work. From a genetic point of view, certain conclusions may perhaps also be drawn from a comparison between variations in natural radiation at the earth's surface and the artificial irradiation of the population. The lack of information regarding the amount of radiation which may be considered completely harmless justifies a closer study of such variations.

The Composition of Natural Radiation

Natural radiation causing ionization and excitation effects in living cells arises mainly from three different sources: cosmic rays, radiation from radioactive elements in the organism itself and the γ- and β-radiation originating from small amounts of radioactive substances in the earth's surface down to a depth of some decimeters and millimeters respectively. These amounts also include disintegration products of radon emanating from deeper layers of the earth crust.

At the earth's surface, cosmic radiation corresponds to a dose rate of about 0.0008 r/week (2.5 ion pairs/cm^3 sec). The radiation is nearly constant if variations during shorter intervals are not taken into account. Since the average ionization density per cm for the particles generated by the cosmic radiation at sea level is of the same order of magnitude as that of γ-rays, there is no reason to presume that cosmic rays are more effective than γ-rays in producing biological actions. The dose rate in the body due

Submitted for publication, Nov. 30, 1951.

to cosmic radiation thus can be considered to be approximately 0.001 rem/week.

The content of radioactive substances in the organism is not very well-known. Some authors (8) have, for instance, found the total quantity of radium in the body to be less than 5×10^{-10} g while other workers (9) have reported values 10 to 100 times larger. Additional measurements employing improved instrumentation are required before it will be possible to estimate with sufficient accuracy the average dose per week due to the radium (and thorium) content. Assuming a rem/rep ratio of 10, because of the α-radiation, and at least 10 times smaller concentration of radium in soft tissue than in the skeleton, the average dose rate in soft tissues can, however, be assumed to be less than 0.001 rem/week. The average content in the body of ca. 0.2 % potassium adds an additional 0.0005 rem per week.

The storage of radioactive substances, especially radium and probably thorium, in the skeletal tissues of the body almost certainly results in an increase in these elements as the individual grows older (15). Large variations may be expected, depending on the content of radioactive elements in the drinking-water and food at the place where the individual has lived. It is obvious that these circumstances are connected with the third of the above-named natural radiation sources, namely, the radiation caused by the radioactivity in the earth's crust.

Naturally Occurring Radiation from the Earth's Crust

The content of radium, thorium and potassium in certain minerals is shown in Table I.

Table I

Mineral	g Ra^{226} per g · 10^{12}	g Th^{232} per g · 10^{6}	g K^{39} per g · 10^{2}
Igneous rocks:			
Average (12)	1.3	12	2.6
Acidic rocks: >65 % SiO_2			
Granites (4)	3.1	20	3.4
Quincy granite (3)	1.0	9	3.9
Younger granites (max. values) (4)	6.5	59	5.1
Granodiorit (4)	2.7	18	2.5
Medium rocks 65—55 % SiO_2			
Diorit (4)	1.4	6	1.7
Basic rocks <55 % SiO_2			
Gabbro (4)	0.83	5.1	0.7
Ultrabasic rocks			
Periodit (4)	0.52	3.3	0.8
Sedimentary rocks:			
Clay	1.5 (5)	11 (5)	2—3 (9)
Sandstone	1.4 (5)	5 (5)	1.1 (9)
Limestone	0.9 (5)	<1 (5)	0.3 (9)

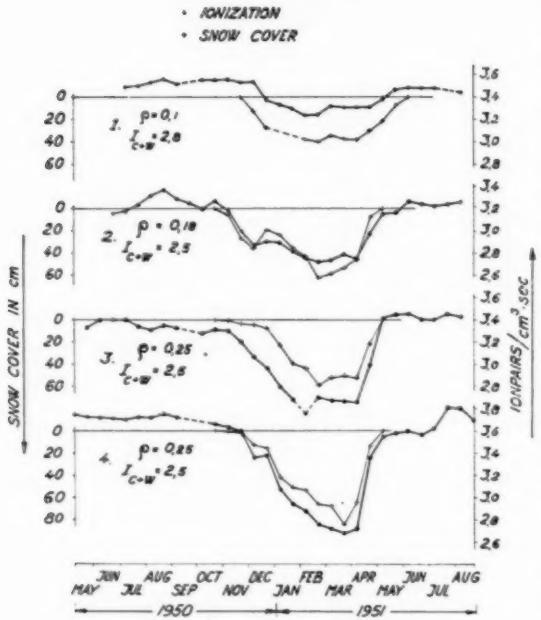

Fig. 1.

The γ-ionization out of doors has a large degree of variation not only due to the concentration of the radioactive elements in the surface layer of the ground, but also with regard to the absorption in a snow cover. Using a pressure ionization chamber having a volume of about 40 l and containing N_2 at a pressure of 7 atmospheres, the correlation between γ-radiation and snow cover was tested at four different places in Sweden. The results are shown in Fig. 1.

The discrepancies found in Place 3 are probably due to an unequal local distribution of snow. A calculation taking into account the volume weight of the snow layer gives the results shown in Fig. 2. The cosmic radiation is not included in these data.

The effect of the ionizing particles from the walls of the ionization chamber together with the cosmic rays causes an average ionization which can be considered to be of the magnitude given by the figures I_{c+w} in Fig. 1. The higher value of I_{c+w} for Place I is caused by the fact that it is situated at a greater altitude above sea-level than the other localities.

Using the data in Fig. 2, the density of the maximum snow-cover at the four places has been calculated to the values indicated by ϱ in Fig. 1. Because of the continuous cold weather at the northernmost latitudes, the snow-cover has a lower volume weight at higher

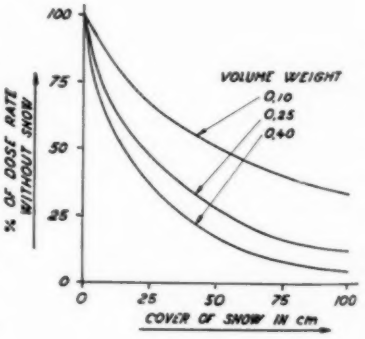

Fig. 2.

latitudes. As the densities found are of reasonable magnitude, the observations seem to be in satisfactorily good agreement with the calculations.

By means of the constants given in Table I, the ionization over different kinds of surfaces has been estimated. The results of the calculations are collected in Table II.

Table II

Calculated values for the ionizations produced by various minerals

Ionization expressed in ion pairs/cm³ sec.
Ionization values corrected for scattered radiation for each mineral are given in the second row of figures in the last columns.[2]

Mineral	Ionization due to content of					Total ionization		
	Ra	Th	K[1] (19)	K (11)	K (2)	(19)	(11)	(2)
Igneous rocks:								
Average	0.8	0.7	1.2	0.7	1.3	2.6	2.2	2.7
						3.1	2.6	3.2
Acidic rocks: >65 % SiO_2								
Granites								
Average	1.8	1.2	1.5	0.9	1.8	4.5	4.0	4.7
						5.3	4.7	5.5
Quincy granite	0.6	0.5	1.7	1.0	2.0	2.8	2.3	3.1
						3.3	2.7	3.6
Younger granites max. values	3.8	3.5	2.3	1.4	2.6	9.6	8.6	9.9
						11.4	10.2	11.8
Granodiorit	1.6	1.1	1.1	0.7	1.3	3.8	3.4	4.0
						4.5	4.0	4.7
Medium rocks 65—55 % SiO_2								
Diorit	0.8	0.36	0.8	0.46	0.9	2.0	1.6	2.1
						2.4	1.9	2.5
Basic rocks <55 % SiO_2								
Gabbro	0.5	0.30	0.32	0.19	0.36	1.1	1.0	1.2
						1.3	1.2	1.4
Ultrabasic rocks								
Periodit	0.30	0.20	0.37	0.22	0.43	0.9	0.7	0.9
						1.1	0.8	1.1
Sedimentary rocks:								
Sandstone	0.8	0.30	0.50	0.30	0.6	1.6	1.4	1.7
						1.9	1.7	2.0
Limestone	0.5	0.06	0.13	0.08	0.15	0.7	0.6	0.8
						0.8	0.7	0.9
Clay	0.9	0.7	1.1	0.7	1.3	2.7	2.2	2.8
						3.2	2.6	3.3

[1] The three alternatives for the radiation from potassium and for the total ionization refer to the different values of half-life and branching-ratio cited on page 392.

[2] The corrections were made by the use of the formulas of HIRSCHFELDER, MAGEE and HULL (4). Although these formulae are not exactly applicable in the present case they indicate the order of magnitude for the corrections.

The calculations are based on the formula

$$I = 2.63 \cdot 10^{17} \frac{S}{T_{years}\, W} \sum E_i\, n_i\, f_i \text{ ion pairs/cm}^3 \text{ sec} \qquad (I)$$

where $f_i = \left(\frac{{}_e\sigma_a}{{}_e\sigma}\right)_i$ and

S = content of radioactive material in g per g
T_{years} = half-life in years
W = atomic weight
E_i = energy of γ-quantum
n_i = number of γ-quanta of energy E_i per primary disintegration
${}_e\sigma_a$ and ${}_e\sigma$ = the KLEIN-NISHINA-coefficients for the absorption part and the total Compton coefficient respectively.

Equation I leads to the following expressions for the radiation from Ra, Th and K:

$I_{Ra} = 0.565 \cdot 10^{12}\, S_{Ra}$
$I_{Th} = 0.534 \cdot 10^{5}\, S_{Th}$
a. $I_K = 44.1 \cdot S_K{}^{39}$
b. $I_K = 27.3 \cdot S_K{}^{39}$
c. $I_K = 50.7 \cdot S_K{}^{39}$

The three alternatives (a, b and c) for the K^{40}-ionization refer to the following values for the half-life and the branching-ratio.

a. $T_{\frac{1}{2}} = 0.55 \cdot 10^9$ years; % γ = 4 (19)
b. $T_{\frac{1}{2}} = 1.11 \cdot 10^9$ years; % γ = 5 (11)
c. $T_{\frac{1}{2}} = 1.33 \cdot 10^9$ years; % γ = 11 (2)

If the ground is covered with snow, the factor f_i in the formula must be changed to

$$f_i = \left(\frac{{}_e\sigma_a}{{}_e\sigma}\right)_i \left[b\sigma_i\, Ei\, (-b\sigma_i) + e^{-b\sigma_i} \right]$$

where b = the depth of the snow cover
σ_i = the total Compton-absorption coefficient of snow for γ-quanta of energy E_i
Ei = the exponential integral.

Details concerning the formulae will be published by one of us (7).

The total ionization is obtained by adding the contribution of the cosmic radiation (and the wall-effect) which can be assumed to correspond to 2.5 ion pairs/cm³ sec.

A calculation of the ionization at the centre of a room $5 \times 5 \times 3$ m³ gives values about twice as high as the ionization over an infinite surface of the same material (if the thickness of the wall corresponds to a mass per cm² exceeding 50 g).

Measuring Instrument

Earlier, one of us has used hermetically sealed condenser chambers for measurements of the γ-radiation in houses (16, 17). Thanks to the development in the techniques of electrometer tubes and high pressure ionization chambers, it is now possible to construct direct-reading portable instruments which permit comparatively rapid observations with a sufficient degree of accuracy. Such an instrument, consisting of an ion chamber (30 kg/cm² N_2, volume ca. 8 l) connected to a VX 41 tube and a reading device containing a compensation circuit together with a well-damped microammeter (0—2 μA), has been constructed. Measurements can be made either by compensation of the anode current and the reading of the number of ion pairs per cm³ per sec directly on an ordinary indicator instrument or by observations of the microammeter deflection. The wiring diagram of the instrument is shown in Fig. 3.

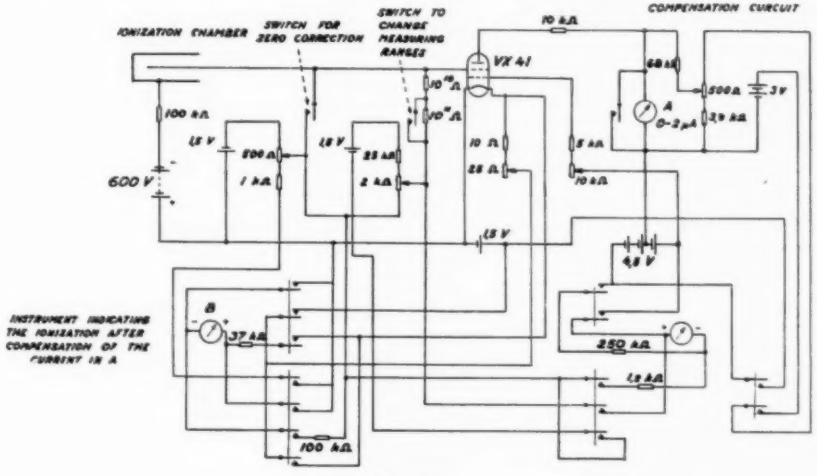

Fig. 3.

Figures 4 and 5 show the instrument ready for use and for transport.

The instrument is calibrated periodically with a radium preparation and after every trip it is checked against a radium standard. Determination

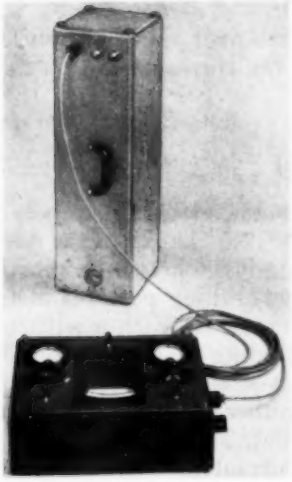

Fig. 4.

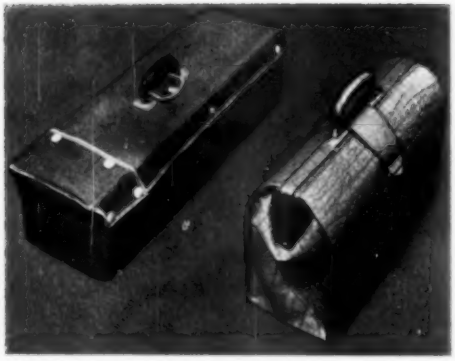

Fig. 5.

of the ionization caused only by the radioactivity of the chamber walls and the cosmic rays was also made by placing the chamber in a water-tank so that the radiation from the surroundings was screened off in all directions by about 90 cm of water. The result corresponded to an ionization of 2.5 ion pairs/cm³ sec.

About one half to one minute is required to make a determination. No disturbances have been observed after transport if the weather is not extraordinarily moist or cold (no drying substance is used); in such cases, the high resistance connected to the grid has been found to change. The constancy of the readings is satisfactory over long periods and the chamber may be used vertically as well as horizontally.

Measurements

Preliminary investigations have been made out of doors and in 68 houses in Stockholm. The observations were undertaken primarily to obtain a general idea of the utility and reliability of the method and also to determine the order of magnitude of the γ-radiation in houses constructed of different building materials. More extensive measurements are planned.

The results of these determinations are summarized in Tables III and IV.

The cause of the high values obtained in houses built of material 3 will not be discussed in detail in this communication; it will only be poin-

Table III

Numbers of houses	Construction	Highest observed values in different houses			Values in the centre of the rooms		
		Max.	Min.	Average	Max.	Min.	Average
10	Wood	7.0	5.0	6.0	6.5	4.8	5.9
10	Bricks or concrete, Type 1 ...	9.5	7.0	8.5	9.0	6.5	8.1
38	» 2 ...	11.0	8.5	9.5	9.0	7.0	8.4
10	» 3 ...	30.0	19.5	25.5	22.5	17.5	16.7

Table IV

Locality	Ion pairs/cm³ sec.
In streets of Stockholm	6.9— 8.5
Over igneous rocks	5.8—10.2
Over clay ground	5.3

ted out that there is reason to believe that the background radiation in certain houses in Sweden is still higher than that hitherto found.

If we subtract the cosmic radiation part of the ionization from the values of Table III and divide the result by two, we find values lying between the limits which are to be expected from the calculated ionization of Table II. The observed radiation corresponds to a dose of 0.002—0.010 rem/week.

The datas in Tables III and IV make it appear probable to us that the natural γ-radiation in Sweden may cause a dose in the human body varying between 0.002 and 0.020 rem week. Consequently, in those parts of the body where radium or thorium are not stored in larger quantities the γ-radiation from the surroundings will be representative for the ionization in the tissue. This must, for instance, be the case in the sex glands.

Discussion

It may be said in general terms that every step should be taken to prevent ill-health even when the incidence of illness is low. It is often considered, perhaps especially by physicists, that the problem of radiation hazards at very small doses, and particularly its genetic significance, is only of academic interest. However, this is the same as saying that a rare or not very serious malady, about which knowledge is incomplete, should be disregarded.

General health disturbances caused by small amounts of radiation are difficult to assess and investigate objectively. But the radiologists' and the irradiated patients' feeling of tiredness and the occurrence of blood changes after very small doses of radiation are well-known facts. A fictive

example will show the possible implications from a practical point of view. Let us imagine that 200,000 of the Swedish population are irradiated every year in not absolutely necessary medical roentgen diagnostics and therapy and in using radioactive isotopes. This radiation may be assumed to result in a 20 % reduction in the working capacity during three months of the year for 10 % of them. In the individual case, such a reduction in the working capacity would probably rarely by noticed and only in very few cases would its association with irradiation be realized. Nevertheless, the figures assumed imply a loss of 1,000 persons' work during the whole year.

The data on background radiation presented in this study may suggest a way to obtain further information for a possible correlation between radiation level and general health conditions. A comparative study of the health conditions of persons living in houses with high and low background radiation seems to us to be a means of contributing to the knowledge of the action of small irradiation doses. The fact that there are many houses in Sweden which are similar in practically all respects excepting background radiation facilitates such an investigation. It should be pointed out that, owing to the difficulties of accommodation, most of the population has lived in the same houses during the past 10 to 20 years.

According to recent investigations by W. RUSSEL (14), the *genetic significance of small doses* of ionizing radiation in man seems to be more important than was earlier believed. This is because the mutation rate per locus has proved to be much higher for mammals (mice) than for Drosophila. Some geneticists (1, 12) are of the opinion that an increase in the mutation rate will give a continuously rising fraction of persons with slight anomalies, such as disturbances in function of various organs, allergies and other partially incapacitating effects. These anomalies will, like the general action of radiation, result in a reduction in the working capacity of the individual.

A comparison of variations observed in background radiation with doses caused by the use of roentgen rays and radioactive substances may be of interest. Using the data obtained from the Swedish supervision of radiological work, we find that, before and during the period of fertility, the dose per inhabitant due to such work is at present of the magnitude of 0.05—0.5 r. This is 0.8—8 % of the average dose caused by background radiation in Sweden. From these figures the conclusion may be drawn that, if 2—20 % of the population were to move from houses having a radiation of say 9 ion pairs/cm³ sec to houses with 6 ion pairs/cm³ sec, the reduction in the amount of ionizing radiation received per inhabitant would be about the same as if all work with artificially produced ionizing radiation or concentrated radioactive substances were stopped. However, not only the latter but also the for-

mer alternative would involve very serious complications. Earlier, one of us (18) expressed the opinion that since the dose received in radiological work per inhabitant is relatively small compared with the variations in the background radiation, they should not be considered to be an important factor in effecting genetic changes in the population. In view of the statements in the present paper, it is doubtful whether this opinion is justified.

If the radiation hazards of the population were a constant factor to which mankind had adapted itself, the danger for coming generations should of course not be very pronounced. However, the rapid increase in the use of ionizing radiation makes such hazards a serious and urgent problem. It may be possible that further investigations will lead to the conclusion that a comparatively small increase in the radiation doses received by the population has a physiological action with an unfavourable influence on health conditions. The consequence would be that the use of building material causing abnormally high background radiation, as well as the use of ionizing radiation not justified by the importance of the medical or economical results attained, would have to be avoided.

SUMMARY

The ionization due to γ-radiation from radioactive substances in the ground is determined by calculation and by measurements. Observations of the γ-radiation in 68 houses in Sweden has shown that the ionization varies between 5 and 30 ion pairs/cm³ sec. There is reason to believe that a more extensive investigation will give still larger differences. The biologic importance of the natural γ-radiation is briefly discussed.

ZUSAMMENFASSUNG

Die durch die Gammastrahlung der im Erdboden befindlichen radioaktiven Substanzen verursachte Ionisation wird durch Berechnungen und Messungen bestimmt. Beobachtungen der Gammastrahlung in 68 Häusern in Schweden haben gezeigt, dass die Ionisation zwischen 5 und 30 Ionpaaren/cm³ sec. variiert. Es liegen Gründe vor, die vermuten lassen, dass eine mehr umfassende Untersuchung noch grössere Unterschiede zeigen wird. Die biologische Bedeutung der natürlichen Gammastrahlung wird kurz besprochen.

RÉSUMÉ

L'ionisation due à la radiation γ des substances radioactives dans le sol est déterminée par calculs et mensurations. L'étude des radiations γ dans 68 maisons en Suède a montré que l'ionisation varie entre 5 et 30 ions couplés/cm³ sec. Il est à prévoir qu'une étude plus poussée donnerait des différences encore plus considérables. L'importance biologique de la radiation γ naturelle est brièvement discutée.

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IS PNEUMO-ARTHROGRAPHY NECESSARY FOR THE DIAGNOSIS OF MENISCUS LESIONS?

by

Aage Wagner

In order to answer the question as to whether arthrography is necessary for the diagnosis of meniscus lesions of the knee-joint, the clinical, roentgenologic and operative findings of 32 patients on whom pneumo-arthrography using KJELD ANDERSEN's technique was performed, have been collected. In all the cases the roentgen examinations and operations revealed lesions of the menisci. 5 patients had no clinical symptoms suggestive of a meniscus lesion but all had a history of trauma. 27 had tenderness associated with trauma; 10 had this symptom only while the remaining 17 also had other symptoms that tended to confirm the diagnosis.

Although the method can be recommended in atypical knee-joint cases, it does not, in the author's opinion, appear to be necessary in ordinary cases, that is to say in those cases in which there are tenderness over a meniscus after a knee-joint lesion. The examination is almost painless and no complications have been encountered. The films are straightforward and easy to interpret.

SUMMARY

In lesions of the knee-joint in which there is tenderness over a meniscus, arthrography does not, in the author's opinion, appear to be necessary. The indications for its exhibition are atypical signs following trauma.

ZUSAMMENFASSUNG

Bei Verletzungen des Kniegelenkes, bei denen Druckschmerz über einem Meniscus vorliegt, scheint nach Ansicht des Verf. die Arthrographie nicht notwendig zu sein. Die Indikationen für ihre Anwendung sind atypische Symptome im Anschluss an ein Trauma.

Submitted for publication Jan. 10, 1952.

RÉSUMÉ

Dans les lésions de l'articulation du genou, qui présentent une douleur à la pression au niveau des ménisques, l'arthrographie est inutile selon l'avis de l'auteur. L'atypie des signes cliniques à la suite d'un traumatisme en serait plutôt l'indication.

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DIFFUSE PAPILLOMATOSIS OF THE URINARY TRACT

by

Cecil Villaume

From time to time cases of papillary carcinoma of the renal pelvis are reported in the literature.

These neoplasms, derived from the epithelium of the renal pelvis, are uncommon and according to MACALPINE (5) the incidence is only 6.4 per cent of all tumours of the kidneys. Occurrences of the tumours are, therefore, worthy of record and the case reported may perhaps be considered of special interest, as it shows, in a unique way, the marked tendency of papillomata to disseminate via urinary passages.

Case History

S. W., a married woman aged 67 (a farmer's wife) was first admitted to the Radium Centre, Aarhus, on April 24, 1949; had always been healthy; stated that her father had died of »cancer of the liver»; family history was otherwise non-contributory.

A few months previously she had begun to complain of occasional renal colic associated with moderate hematuria. A few days before admission she had marked but relatively painless hematuria and the family physician sent her to the local hospital, where she received treatment; a diagnosis of »papillomata of the urinary bladder» was made (the cystoscopic examination had revealed sessile papillomata at the base of the bladder) and these were removed by electro-coagulation.

Physical examination. — The patient was well-nourished, pale but not acutely ill; no palpable tumours noted; blood pressure: 185 systolic, 100 diastolic.

Cystoscopic examination. — Near the ureteral orifices there were small, firm patches of necrosis due to electro-coagulation. In addition a number of minute, villous, velvety tumours were noted in the mucosa of the bladder, especially at the base. Biopsy specimens were taken. *Microscopic examination* showed numerous small particles composed of rather loose connective tissue infiltrated with leukocytes, lymphocytes and plasma cells; the tissue formed papillae covered with stratified squamous epithelium which in most regions resembled the transitional epithelium of the urinary tract. However, cellular pleomorphism was found here and there and the transition between the cells and the connective tissue was not everywhere distinct.

Submitted for publication Oct. 31, 1951.

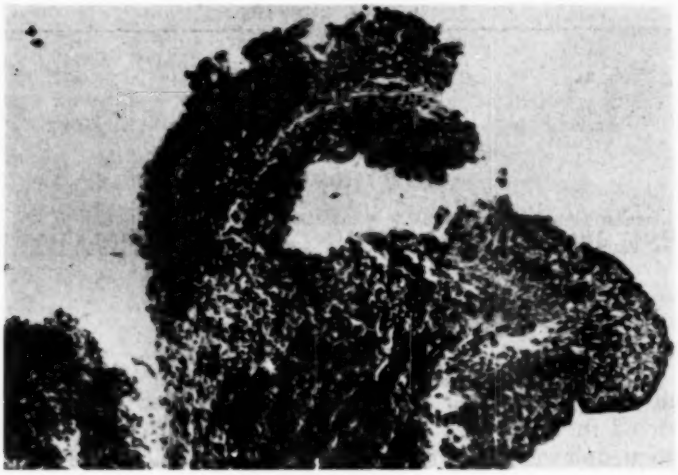


Fig. 1. A photomicrograph of the tumor × 150.

The microscopic appearance thus revealed typical papillomata of the bladder with a tendency to malignant changes (fig. 1). It has to be stressed, however, that biopsy does not provide exact information as to the true nature of bladder tumours (see later).

Repeated *retrograde and intravenous pyelographies* revealed the same uniform changes (figs. 2 a and b). Both kidneys showed good excretion of the contrast (renal parenchyma not invaded). The renal shadows were normal. Both renal pelves and ureters had characteristic appearances: multiple filling defects were seen. The contrast medium presented a foamy appearance. The roentgenologic diagnosis was: disseminated papillary tumours of the urinary tract.

The bladder appeared normal in the radiograms; most of the tumours had previously been removed. The roentgenologic examination of the colon showed no signs of polyposis.

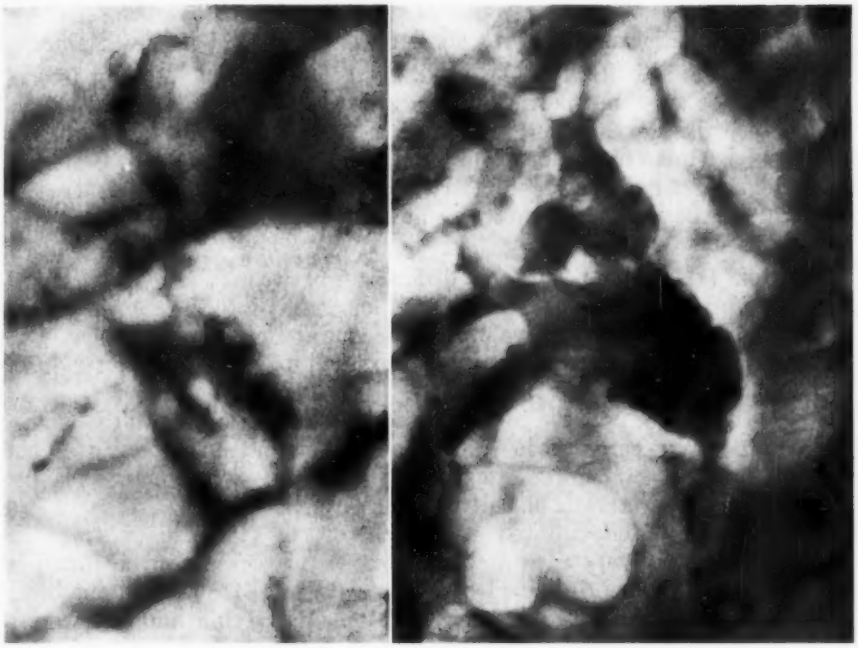
Various laboratory investigations were all non-contributory with the exception of the finding of a slight hypochrome anemia and of erythrocytes in the urine. The blood urea was normal.

Treatment: rotatory irradiation of the bladder (3,600 r in front and 2,400 r behind; »semirotation»). On account of the bilateral diffuse nature of the lesions, surgical treatment was not considered.

Several check-up examinations of the patient have shown her to be in good health: August 1951 ($2^1/_2$ years after the onset of symptoms) a bean-sized recurrence on the left side at the base of the bladder was found and removed by electroresection. Microscopic examination suggested malignancy. A further urographic examination revealed the condition in the ureters and in the renal pelves to be stationary.

Discussion

The case reported exhibits features of special interest in that there is extensive dissemination of papillary tumours throughout the urinary tract.



a. b.

Fig. 2. Urography: Defects simulating air-bubbles in the pelvis and the upper part of the ureter giving the contrast medium a foamy appearance. Similar findings also in other parts of the ureter and in the pelvis and ureter on the other side.

a. Small amounts of contrast in the pelvis.
b. Pelvis distended by large amounts of contrast.

It is a well-known phenomenon that papillomata of the urinary epithelium possess marked powers of metastasis by implantation, and secondary deposits in a part of the ureter or and the bladder are often found.

Some few authors have also recorded cases of bilateral papillomatosis of the renal pelves with secondary growths in one or, more seldom, both ureters. On perusal of the literature, however, cases of bilateral papillomatosis of the renal pelves with secondary deposits in the ureters and simultaneous involvement of the bladder appear to be extremely rare.

MacDonald & Priestley (7) report a total of 75 operated cases of papillary tumours of the renal pelvis, of which not a single one was bilateral. On the other hand, Lower (4) reports a case in which he found

secondary deposits not only in one of the ureters but also in the bladder; the same investigator found 18 similar cases recorded in the literature.

THOMAS & REGNIER (12) found that 23 per cent of all cases of neoplasms of the renal pelvis had multiple growths in one of the ureters or/and the urinary bladder, but only in 4.2 per cent of cases was the renal pelvis (but not the ureter) of the opposite side involved. Generally most investigators report secondary deposits scattered over the mucous surfaces of the unilateral ureter or/and the bladder in 28—50 per cent of all cases.

CAULK (1) pointed out the difference between the *papillary* and *non-papillary* forms of tumours and showed that the non-papillary forms did not as a rule give rise to secondary growths; if there were any extension, then only the most proximal part of the ureter (near the renal pelvis) became involved.

It is thus quite possible to find cases recorded of unilateral dissemination of papillary tumours in the urinary tract and occasionally — but more seldom — come across a case of bilateral involvement (the bladder or part of the ureters is usually not involved).

Such widely disseminated papillomatosis of the urinary tract, as in our patient, is very rare and only one similar case can be found in the literature. It was described by RAYER (9) in 1841, the patient being a 58-year-old woman with the same symptoms (renal colic and hematuria). The post-mortem report read: several small, villous tumours attached by delicate pedicles to the mucous surfaces throughout the renal pelves and ureters; a conglomeration of smaller papillary growths noted in the bladder.

Etiology and Pathogenesis. »Unrestricted» diffuse dissemination of papillary tumours may arouse speculation as to how these growths become scattered over the epithelium of the urinary tract and the tumour-cells become planted and gain a hold.

It would be of interest to know if this peculiar »belligerent» type of tumour is cellular transmissible — and, if so, to test its possible cell-free transmission and find out whether the tumour is due to a virus.

Unfortunately, there was little tumour-tissue to be obtained from the patient's vesica but transplantations into the urinary bladder of rabbits was attempted. The tumour did not »take», however.

As to the simultaneous appearance of multiple tumours in the renal pelvis, the ureter and vesica there are many hypotheses; space allows of only a short presentation.

It should be borne in mind that the pelvis of the kidney, the ureter and the bladder, are so closely related embryologically, functionally and structurally that it is natural that they should exhibit similar

pathological conditions; all are lined by stratified squamous epithelium (»transitional epithelium»).

The earliest theory attempts to explain how the papillomata extend from the renal pelvis along the mucous surface itself, as a sort of »descending dissemination». Against this hypothesis is the fact that secondary deposits may be found in the ureter and in the vesica a long time after the primary tumour in the renal pelvis has been removed. The urinary flow in the ureter has also been considered an essential factor in the spreading-mechanism of these tumours.

The association of cancer of the bladder with certain occupations, such as work in aniline-dye factories, is now a well-established fact. It was described by L. REHN as early as 1895. Certain chemical compounds have been held chiefly responsible for the development of neoplasms of the urinary tract. Of these *Beta-naphthylamine*, in particular, is worth mentioning. Perhaps it would be useful to look for carcinogenic substances in the urine, as already suggested by Rehn.

ROSE (10) has repeatedly found cases of vesical tumours in districts where aromatic amines are manufactured and used.

The effect of aniline is more often observed in the vicinity of the trigone of the bladder, where there is a good blood-supply. In these cases the carcinogenic substances are probably conveyed via the blood-stream. Tumours found near the »internal orifices» rather support a different etiology (secondary deposits via the urinary flow).

An acceptable theory is the one based upon multicentric tumour growth. EWING (2) states that in cases in which an extensive spread of secondary deposits occurs, there must be factors responsible for the dissemination, and which affect the entire epithelium in the urinary tract at the same time. CAULK (1) in this connection speaks of a »cancerogenic irritation» of the epithelium.

Symptomatology, Diagnosis and Treatment. It is important to know how long a patient may remain with relatively minor symptoms. MACALPINE (5) finds the average duration of symptoms before the patient seeks advice to be from a few weeks to about 18 months. Cases have been recorded, however, in which the symptoms persisted for 9—12 years. This agrees with the fact that papilloma of the urinary tract although certainly all potentially malignant, may be benign for several years.

The typical sign — especially in case of involvement of the bladder — is monosymptomatic hematuria.

If papillomata are present in the ureter or renal pelvis, they may give rise to obstruction with subsequent dilatation of the pelvis and contribute in producing renal colic; clots of blood in association with

papillary tumours may also cause obstruction. It is important for the radiologist to note this accompanying hydronephrosis as it may help in distinguishing between papillary tumours of the renal pelvis and a hypernephroma, the latter rarely being accompanied by hydronephrosis.

In cases of papillary tumours in the renal pelvis, cystoscopic examination may not reveal anything abnormal in the bladder with the exception of a bloody, tarry efflux from a ureteric orifice or the margins of the latter may only be a little blood-stained (*Fenwich's sign*).

Urographic examination is very valuable and in most cases will give the correct diagnosis. In the case of minute papillomata, however, the exact diagnosis may be doubtful but may be confirmed by observing the ureteric orifices cystoscopically during an attack of hematuria (Fenwich's sign, above).

The urographic findings have already been mentioned. The foamy appearance of the dye, the serrated contours of the pelves and ureters were characteristic. Filling defects may be masked, however, in advanced cases of hydronephrosis.

A disease for which small papillary tumours in the renal pelvis and the ureter may be mistaken is *pyelo-ureteritis cystica*. Typical of pyelitis cystica is dilatation of the ends of the major calyces and a cystic dilatation of the ureteropelvic junction; small pelvic filling defects may be present in this condition as in papillomata but in the case of the latter the contour of the pelvis has a more serrated appearance in the roentgenogram while in the former the filling defects often take the shape of »mucosal rugae» (cf. ventricular mucosa).

If there is a suspicion of papillomata of the urinary tract and the diagnosis is made before operation it is not advisable to perform any operation which opens the urinary passages, by reason of the danger of sowing secondary deposits in the wound. MACALPINE (5) advocates nephro-ureterectomy in one stage (and removal of the intramural part of the ureter) as the treatment of choice. It should be remembered that secondary growths in a residual ureter and the bladder are common after simple nephrectomy.

Histology and Prognosis. A frequent method of classification of papillary tumours of the urinary tract is to distinguish between the papillary type (75 per cent of all cases) and the non-papillary type (25 per cent).

From a *therapeutical* point of view, however, the best mode of classification appears to be the one suggested by MCDONALD & PRIESTLEY in 1944 (7):

1) papillary tumours without infiltration (50 per cent; five-year survival)

2) papillary tumours with infiltration
3) infiltrative type.

Moreover, it is necessary to take the degree of involvement of the renal vein and its ramifications into consideration. The involvement of the perineural lymphatics also plays a part in assessing the prognosis.

From a histological point of view one may classify the epithelial neoplasms of the renal pelvis thus:

I) papillary type — papillomata (»benign») / papillary carcinoma or »epithelioma» (infiltrating or non-infiltrating)

II) non-papillary type (or »solid») — transitional cell / squamous cell type (SWIFT-JOLY)

III) alveolar carcinoma (of EWING)

In the extensive work of SWIFT-JOLY (11), in which he reports 337 cases of papillary tumours of the urinary tract, the distribution of the various types was as follows: 120 »benign» papillomata, 138 papillary carcinomas, 50 squamous-cell type and 29 transitional-cell type.

In evaluating the prognosis it is necessary to take into consideration the histology of the tumour in question (including the grading of malignancy according to Broders' principle).

Papillary carcinoma has a bad prognosis. According to PRIESTLEY (8) operative treatment yields 35 per cent five-year survivals and 10.5 per cent ten-year survivals.

The rarer non-papillary or solid type growth has a rather hopeless prognosis; HIGGINS (3) found no patient without metastases five years after treatment (squamous-cell type). The five-year survival rate, therefore, is poor in the two above-mentioned types and the rate for combined treatment (surgical and radiological) is only a little better.

The so-called benign papillomata generally have a far better prognosis. MACALPINE (5) has been able to follow certain patients for 23 years after the onset of symptoms.

However, these »benign» papillomata may behave in an insidious and incalculable way and it is safer, in assessing the prognosis, to be cautious; papillomata are prone to develop into malignant tumours. Even if the microscopic examination shows a »benign papilloma», one must be on the alert, as the degree of malignancy may vary in different parts of the same tumour.

Neoplasms arising from the transitional epithelium or originating in patches of leucoplakia (squamous-cell tumours) of the urinary tract occupy a particular position among tumours in general. They appear to be well worth further study and investigation.

SUMMARY

A case of diffuse papillomatosis of the renal pelves, both ureters and urinary bladder is recorded. Radiologic and histologic findings are mentioned and illustrated. Papillomatosis of the urinary tract is discussed.

ZUSAMMENFASSUNG

Ein Fall mit diffuser Papillomatose der Nierenbecken, beider Ureteren und der Harnblase wird berichtet. Die radiologischen und histologischen Befunde werden erwähnt und illustriert. Die Papillomatose der Harnwege wird diskutiert.

RÉSUMÉ

L'auteur présente une observation de papillomatose diffuse des bassinets, des deux urétères et de la vessie, avec examens radiologique et histologique; il étudie particulièrement certains problèmes étiologiques, cliniques et thérapeutiques de la papillomatose urinaire.

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ON ACNE VULGARIS

and its Treatment with Bucky Rays

by

O. Kaalund-Jorgensen

Acne vulgaris (A. v.) is a disorder with which general practitioners as well as radiologists and dermatologists often have to deal. Even though the condition is not serious and, untreated, tends to disappear after some years, it often has a serious psychologic effect on the patient because his appearance suffers considerably. This psychological influence manifests itself in the so-called neurotic excoriations, for example, which develop because the patient keeps on scratching and picking the acne lesions.

A. v. is a disorder of puberty and is often called *acne vulgaris juvenilis*. According to BLOCH, A. v. very frequently occurs as early as the age of 10 years, being more common among boys than girls, and usually disappears in the late twenties. LIPMAN COHN states that in women it mostly occurs between the ages of 19 and 21 and frequently persists into the thirties. In men it occurs most frequently between 18 and 23.

Common acne originates in the excessive activity of the sebaceous glands, especially in the seborrhoeic skin areas (face, chest and back; EMANUEL, KVORNING). This excessive activity is undoubtedly due to hormonal disturbances (development at puberty, spontaneous disappearance later (BLOCH); furthermore WILE, BARNEY & BRADBURY and LAWRENCE & WERTHESSEN state that a decreased urinary estrogen excretion may be observed in A. v. patients). Owing to the considerable secretion of sebum, comedones develop; these are later infected with acne bacilli and staphylococci, resulting in the formation of acne pustules.

According to numerous authors (int. al. ROST & KELLER; KILE, SNYDER & HAEFLE), intestinal disturbances and the eating of certain foods and sweetstuffs, such as fats or chocolate, may help to bring on A. v. In the author's opinion, their influence is very small, and his view is borne out for example by the fact that the incidence of A. v. in Denmark did not decline during World War II, when fats were rationed and chocolate unobtainable. Occasionally, however, isolated acne pustules do occur following meals with a particularly high fat content.

Submitted for publication, March 3, 1952.

In women with a tendency to seborrhoea, the injudicious use of cosmetics may be a contributing factor. This applies especially to the so-called skin-nourishing creams, and, in particular, to those containing mineral oils, since it is well-known that vaseline vapours may give rise to an acneiform skin affection (the so-called vaselinoderma).

Clinical Types

Acne has been subdivided into various clinical types. In the author's opinion we need only distinguish between three: *Acne superficialis* (which is by far the most frequent), in which the comedones are the predominant feature and the acne pustules rather superficial and causing no great scarring provided the patients refrain from picking the lesions (neurotic excoriations); *Acne profunda*, characterized by larger, more deep-seated sebaceous cysts which later become infected; these contain thin pus or a jelly-like fluid and often reproduce themselves after being evacuated; they may leave marked, often keloid-like scarring (acne keloidea); finally, *Acne conglobata*, also characterized by more deep-seated pustules — generally on the trunk (especially the back) —, by double comedones and by its very protracted course.

Treatment

Innumerable methods have been employed in the treatment of A. v. As already mentioned, it is the author's opinion that *diet*, etc., plays a very subordinate rôle. Treatment with *vitamin B* (yeast) also appears to be quite ineffective. A number of the author's patients had been taking large amounts of this remedy for lengthy periods without the slightest effect. *Vaccine treatment* (acne staphylococcus vaccine, autogenous vaccine, »Reoderm», etc.) also appears to have no definite effect; it also seems to be ill-advised, since it is directed only against the secondary infection and not against the causative factor, *i. e.*, the increased secretion of sebum. *Penicillin therapy* (in the form of injections or as ointments) also appears to have no value although it seems that *bismuth* injections may have some effect on the deep-seated forms of acne.

Favourable results are reported of *treatment with estrogenic hormones* given orally (GOECKERMANN, and WAY & ANDREWS) but not as local treatment (LYNCH). Hormone treatment appears to be logical but has hardly been sufficiently tried out; moreover, in the author's opinion it is not entirely devoid of risk. It is therefore considered advisable to await further reports before this therapy is adopted, except in cases where there is a distinct exacerbation immediately prior to, and during, menstruation (*acne menstrualis*).

The object of the treatment in A. v. should be to achieve a slightly *desiccative* and disinfectant effect. This object can be attained partly by *local treatment* with a paste or lotion and partly by *physical therapy*.

In local treatment, sulphur has been the principal remedy since olden times. It may be employed together with resorcinol in a paste (resorcinol g. 3, dissolved in glycerin g. 6, sulphur precipitatum g. 2, pasta lanolinata ad g. 40), applied in the evening and washed off with soap and water next morning. Lotions such as linimentum sulphuris Vidal or »Euthiosol» have a milder effect. Only a very few patients do not tolerate sulphur.

It is an important feature of the local treatment that the patient himself should express the comedones daily with a comedo extractor, and that the physician should express the comedones at every consultation, puncture the acne lesions with a pointed knife, and squeeze them cautiously. In specially stubborn cases, where the comedones are numerous, the use of a »peeling» paste may be advised (sapo fuscus g. 17, cretae pulveratae, sulphur precipitatum aa g. 5, pyroleum pini g. 3, Sig. »peeling» paste to be used for 3 hours at a time and then washed off). The patient should be warned against using any kind of cream; face powder, however, does not appear to have any harmful effect.

Physical Therapy. Most acne patients show improvement in summer, and this is no doubt due to the desiccative action of the ultraviolet rays on the seborrhoeic skin. It was therefore natural to attempt the treatment of A. v. with *artificial ultraviolet light*, and excellent results have been reported from carbon arc light treatment (KISSMEYER) and mercury quartz light too (WERTHEIM, THEDERING, BUTLER). This form of treatment, however, makes great demands on the patients' time (2 or 3 exposures a week for about three months being required), and the improvements have not been particularly lasting (LOMHOLT, ANDREWS).

It has been established (HALBERSTÄDTER) that *Roentgen irradiation* reduces the function of the sebaceous glands. Roentgen therapy has therefore been employed in the treatment of A. v., and satisfactory results have been reported (HABERMANN & SCHREUSS (cited STEIN); BELISARIO; ANDREWS; KLINE & GAHEN). In general, rather hard rays (produced by tensions around 100 kv) and small fractional doses have been employed. Even so, the treatment does not appear to be entirely without risk. ANDREWS, for example, states: »Epilation and erythema are always evidence of excessive treatment and must be avoided, as they are almost invariably followed by atrophy or teleangiectasis.» The total dose, according to this author, must not exceed 1,200 r within one year, and he advises against a total dose of over 800 r in most cases. The author considers however this dose to be far too high, in view of the hard quality of the radiation.

Grenz rays introduced by BUCKY, however, (also called ultrasoft Roentgen rays, or usually *Bucky rays*) (BUCKY; SCHREUSS; EBBEHOJ), when used in a suitable dose, appear to involve practically no risk, as they are able to penetrate only the most superficial part of the dermis (just where the sebaceous glands are situated). In dermatologic therapy, Bucky rays, strangely enough, appear to be very seldom used except in Germany and the Scandinavian countries, although excellent results in A. v. have been reported from these countries by BUCKY, SCHREUSS, KISSMEYER, LOMHOLT and KLEM.

Author's Material

From 1944 to 1950 the author privately treated 270 A. v. patients.

Acne vulgaris superficialis

233 patients (167 women and 66 men) had A. v. superficialis. 80 patients (46 women and 34 men) visited the author only once or twice and were treated either with ointment alone or with a single Bucky irradiation; for this reason these 80 patients are not included in the evaluation of the results of the treatment. A survey of the material and age-distribution is shown in Table 1.

Table 1

Acne vulgaris superficialis

Age	Female	(Treated with Bucky rays, whole course of treatment)	Male	(Treated with Bucky rays, whole course of treatment)	Total	
10—14	8	(7)	3	(1)	11	(8)
15—19	52	(43)	30	(16)	82	(59)
20—24	53	(36)	17	(9)	70	(45)
25—29	35	(22)	12	(3)	47	(25)
30—39	14	(11)	4	(3)	18	(14)
over 40	5	(2)	—	—	5	(2)
Total	167	(121)	66	(32)	233	(153)

These figures do not permit definite conclusions to be made about the incidence of A. v. in the two sexes: the disorder has a more pronounced psychologic effect on women than on men; hence more women seek medical advice. This accounts for the fact that while almost three-fourths of the women went through the whole course of treatment, not quite half of the men did so. It will be seen from the material that A. v. does not always disappear at about the age of 25: 30 per cent of the patients were over 25 years of age, and 10 per cent were over 30. Acne vulgaris rarely seems to occur after the age of 40.

No material is available about untreated controls. This does not really affect the present series, since on an average the patients had been

sufferers for about 3 years before seeking the author's advice, and most of them had tried various forms of treatment; about 13 per cent had received mainly vitamin B preparations; about 4 per cent, vaccine treatment; about 31 per cent, only local treatment — mostly with sulphur preparations; about 17 per cent, mercury quartz radiation; about 2 per cent, Bucky treatment; the remaining patients, about 33 per cent, had received no particular treatment.

The principles of the author's treatment were as follows:

a) Prohibition of cosmetic creams.

b) As regards dietetic measures, simply a warning against eating chocolate and foods with a high fat content.

c) Application of a sulphur resorcinol paste (see p. 411) in the evening, washed off with soap and water next morning.

d) In stubborn cases, the use of »peeling» paste (p. 411).

e) At each consultation (at intervals of one or two weeks), expression of comedones and puncture and evacuation of the acne pustules.

f) Bucky irradiation by the method described by LOMHOLT. A Siemens' Bucky apparatus was used: 12 kv, 10 ma, skin-target distance, 6 cm, 200 to 300 r given usually at intervals of 2 weeks. Individual patients received from 3 to 7 exposures, 4 radiations being sufficient in most cases.

Side-effects in this form of therapy were extremely rare. Only a very few patients did not tolerate sulphur or resorcinol; they were treated with sulfathiazole paste instead.

Among the side-effects of the Bucky treatment may be mentioned pigmentation; it is seen most frequently, of course, in dark-skinned persons. Such pigmentation is, in most cases, very mild; if the treatment be properly conducted, the pigmentation is uniformly distributed. In two cases, intense pigmentation appeared on the neck because the radiation fields had overlapped. Pigmentation does not signify any permanent roentgen injury: it always disappears fairly rapidly and does not necessitate discontinuation of the Bucky treatment; all that is required is a decrease in dose, or a short pause in the treatment, and shielding the neck, for example, when the face is being irradiated.

In two patients the Bucky treatment produced a slight irritation of the face, with erythema and subsequent peeling. The symptoms disappeared within a few weeks. Only in one case did a severe Bucky dermatitis develop on the back, necessitating admission to hospital. The author finds that the skin of the back does not tolerate such large doses as the face; for this reason he does not advise more than 200 r at each exposure to the back.

In no case was there lasting roentgen injury to the skin, or any approach to teleangiectasis or scarring, even following a total dose of 3,000 r within one year.

The *results of the treatment* were excellent in almost all cases; after a few exposures the number of comedones greatly decreased, and but few, quite superficial, acne pustules developed. Of the 153 patients who underwent the whole course of treatment: the skin of 109 (71 per cent) had practically cleared up on discharge; in 35 (23 per cent), the skin had cleared up well, but small eruptions continued to occur; and 9 patients (3 per cent) were unimproved. In 23 cases (16 per cent) there were slight relapses, usually not till a year afterwards; almost all these relapses yielded readily to one or two further Bucky irradiations.

Acne vulgaris profunda.

Altogether 37 patients (22 women and 15 men) with *acne vulgaris profunda* were treated by the author. The distribution is shown in Table 2.

Table 2

Acne vulgaris profunda

Age	Women	Men	Total
15—19.....	4	7	11
20—24.....	7	5	12
25—29.....	7	1	8
30—39.....	3	2	5
over 40.....	1	—	1
Total	22	15	37

The principles of the treatment were partly the same as for acne vulgaris superficialis, except that, in addition, 27 of the patients were given bismuth injections (20 centigrams of Bi in oily suspension, administered intramuscularly once a week — in most cases a total of 10 injections). The results of treatment were not so satisfactory as those achieved in acne vulgaris superficialis, probably partly owing to the fact that the Bucky rays cannot penetrate into the deep-lying lesions, and partly because the aetiology of acne vulgaris is somewhat different (tendency to formation of small sebaceous cysts with infection and necrosis). Of the 37 patients with acne vulgaris profunda, 11 were cured; in 20, the skin had cleared up well, but eruptions continued to develop, although in considerably smaller numbers than previously; 6 patients remained unimproved.

SUMMARY

After reviewing the symptoms of acne vulgaris and the various methods of treatment described in the literature, the author reports his results with a method of treatment, the principles of which were laid down by LOMHOLT. The therapy employed con-

sists in local treatment with sulphur resorcinol paste, puncture and expression, and Bucky irradiation. The author concludes that the treatment involves no risk, is speedy, and cures about 70 per cent of cases of A. v. superficialis. In A. v. profunda, the treatment was generally supplemented by bismuth injections. The results obtained in this type of acne were not quite so satisfactory.

ZUSAMMENFASSUNG

Nach einer Übersicht über die Symptomatologie der Acne vulgaris und über die verschiedenen in der Literatur beschriebenen Behandlungsmethoden berichtet der Verf. eigene Resultate mit einer Behandlungsmethode, deren Prinzipien von LOMHOLT festgelegt worden sind. Die angewendete Therapie besteht aus Lokalbehandlung mit Schwefelresorzinolsalbe, Punktion und Ausdrückung sowie Buckybestrahlung. Der Verf. zieht den Schlussatz, dass die Methode keinerlei Gefahrenmomente enthält, schnell durchführbar ist und etwa 70 % aller Fälle von A. v. superficialis ausheilt. In Fällen von A. v. profunda wurde die Methode mit Wismuthinjektionen ausgebaut. Bei diesem Acnetypus waren die Heilungsresultate nicht ganz so zufriedenstellend.

RÉSUMÉ

L'auteur passe en revue les symptômes de l'acné vulgaire et les diverses méthodes de traitement décrites dans la littérature, puis rend compte des résultats qu'il a obtenus avec une méthode de traitement dont les principes ont été posés par LOMHOLT; cette méthode consiste en traitement local avec une pâte au sulfate de résorcine, ponction et expression des pustules et rayons de Bucky. Selon l'auteur le traitement ne comporte aucun danger, est rapide et guérit environ 70 pour cent des cas d'a. v. superficielle. Dans l'a. v. profonde, le traitement fut en général complété par des injections de bismuth. Les résultats obtenus dans ce type d'acné n'ont pas été aussi satisfaisants.

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NORTHERN ASSOCIATION FOR MEDICAL RADIOLOGY

Preliminary Programme

of

THE EIGHTEENTH CONGRESS IN HELSINGFORS

JUNE 9TH—11TH, 1952

Monday, June 9th:

11 a.m. Meeting of the Board of the Northern Association for Medical Radiology.

3 p.m. General meeting at FINSKA HANDELSHÖGSKOLAN, Runebergsgatan 14—16.

8 p.m. Reception at Stockmann's Restaurant, Centralgatan 2. The foreign members of the Congress will be the guests of the Finnish Radiological Society.
Informal dress.

Tuesday, June 10th:

9 a.m. Opening ceremony at FINSKA HANDELSHÖGSKOLAN.
The Gösta Forssell lecture (Gösta Jansson, Helsingfors).
Scientific meetings.
In the evening foreign members are invited to a social gathering.

Wednesday, June 11th:

9 a.m. Scientific meetings.
Closing session.

7 a.m. Congress dinner at the Brändö Casino. (Dinner jacket.)

A special programme for the ladies will be announced later.

1. **Notification** *of attendance at the Congress and for reservation of hotel accomodation* should be submitted before May 1st to the Congress Bureau. In exceptional cases notifications will be accepted until May 15th, but after this date accomodation cannot be guaranteed because of the Olympic Games. Congress fee (including wife or husband) Fmk. 1000:—.

2. **Notification** *of papers* to be read will be accepted until May lst. A short summary for publication should be enclosed. Communications must not exceed 10 minutes (in exceptional cases 15 minutes). For contributions to discussion 5 minutes are allowed. A projecting apparatus for slides 8 × 8 cm. and larger, and epidiascope pictures up to 20 × 20 cm., and a 16 mm. and 35 mm. film projector are available.

The following subjects will be treated in detailed lectures:
Diagnosis and radiotherapy of cancer of the lung (S. Mustakallio, Helsingfors).
Cholangiography (Olof Norman, Lund).

Until June 9th the address of the Congress Bureau is: Strålbehandlingsinstitutet, Unionsgatan 38, Helsingfors (Dr. K. Malmio).

During the congress: Finska Handelshögskolan, Runebergsgatan 14—16. Open from 9 a.m., June 9th.

We lock forward to a large gathering at the Congress and extend a cordial welcome to our Northern colleagues.

Sakari Mustakallio
President

Karl Sandström
Secretary-General

Kai Malmio
Secretary

Karl-Erik Johanson
Secretary

THE THIRD
SYMPOSIUM NEURORADIOLOGICUM

WILL BE HELD IN STOCKHOLM

ON SEPTEMBER 17TH – 20TH, 1952

AT »RIKSDAGSHUSET» (HOUSES OF PARLIAMENT).

Scientific programme: Scientific sessions 17th, 18th, 19th and 20th September. One session will be held jointly with the Scandinavian Neurosurgical Society. Theme for discussion: Encephalography in cases of intracranial tumour.

The following papers will be read:

ANDERSSON, T. (Stockholm): Roentgen diagnosis of meningiomata of the falx.

BOURDON, FISCHGOLD, Mme GILLES, HERDNER, LENZI, LOMBARDI, MASCHERPA, OLIVA, PIAZZA, PORCHER, VALLEBONNA (Paris, Bourges, Modena, Milano, Genova): Tomographie cranienne en neuroradiologie.

BULL, J. (London): The radiological diagnosis of spinal meningiomas and neurofibromas.

CHILDE, A. (Winnipeg): Five unusual cases with lesions in the cerebellar fossa.

DECKER, K. (München): Gefässverlagerung bei Stammgangliontumoren und Tumoren der hinteren Schädelgrube bei der Vertebralis-angiographie.

FALK, B. (Stockholm): Encephalography in cases of intracranial tumour.

FISCHGOLD, H., DAVID, M., TALAIRACH, J. and BRÉGEAT, P. (Paris): Opacification directe du système veineux du crâne, du cerveau et de l'axe rachidien; essais pratiqués dans le service de neurochirurgie du Dr. David, à Paris.

FREDZELL, G. (Stockholm): Apparatus for serial angiography.

GVOZDANOVIĆ, V. and REISSNER (Zagreb): Angiographic studies of brain revascularization.

HOARE, R. (London): Some cases of arterio-venous aneurysms of the posterior fossa.

JOHANSSON, C. (Stockholm): The cerebral phlebogram.

LENZI, M. (Modena) and MASCHERPA, F. (Milano): Perfectionnements techniques dans l'examen stratigraphique du crâne et de la colonne vertébrale.

LINDGREN, M. (Lund): Roentgen therapy of gliomata.

LOMBARDI (Milano): L'examen stratigraphique des citernes de la base.

LÖFGREN, O. (Lund): Carotid angiography in the diagnosis of spontaneous intracerebral haemorrhage.

LÖFSTEDT, S. (Stockholm): Angiography in intracranial arterial aneurysms. Further investigations.

MASCHERPA, F. (Milano): L'examen stratigraphique de l'ethmoïde et de la lame criblée. Résultats.

MOXON, C. P. (Manchester): Intracranial meningiomata. A review of experiences in their radiological investigation at Manchester Royal Infirmary.

ODÉN, S. (Stockholm): The radiological diagnosis of spinal tumours by means of gas myelography.

OLSSON, O. (Lund): Vertebral angiography.

MCRAE, D. L. (Montreal): Bony abnormalities in the region of the foramen magnum: comparison of the pathological and clinical findings.

REID, R. (Manchester): »Intracranial aneurysms», experiences in their radiological investigation.

Sanchez-Perez, J. H. (Hollywood): Demonstration of a Seriograph.
Sheldon, Ph. (Oxford) and Wickbom, I. (Göteborg): Some aspects of the radiological diagnosis of suprasellar and posterior fossa lesions.
Sheldon, Ph. (Oxford): A cine radiographic investigation of air encephalography.
Sjögren, S. E. (Stockholm): Percutaneous vertebral angiography. A review of 250 cases.
Sutton, D. (London): Pontine gliomata.
Ziedses des Plantes, B. G. (Rotterdam): Ventriculography with small amounts of air.

There will be time for discussion after every paper.

Scientific exhibition will be arranged on the ground floor of »Riksdagshuset» (Houses of Parliament) in connection with the technical exhibition.

Technical exhibition. Manufacturers of roentgen apparatus, contrast media, roentgen film, neurosurgical instruments etc. from different countries will exhibit in »Riksdagshuset» (Houses of Parliament).

Social programme. Reception at »Stadshuset» (Town Hall of Stockholm) the 16th of September. Excursions. Performance at the Drottningholm Court Theatre. Banquet.

Participation. All those wishing to attend the Symposium are requested to send in their names and addresses to the Secretary as soon as possible. They will then receive the detailed programme and an application form. Applications both for the Symposium and for hotel rooms *must* be submitted before July 1st. 1952. Accomodation in Stockholm is rather limited, but the utmost will be done to make suitable arrangements, and fulfill the members' wishes as far as possible.

Fees. The Symposium fee is Sw. Kr. 100:– for participants and Sw. Kr. 30:– for family members. The price of the banquet is Sw. Kr. 35:–.

Symposium fees should if possible be paid into the account of »Symposium Neuroradiologicum», Svenska Handelsbanken, Stockholm.

The Symposium Committee welcomes radiologists, neurosurgeons and neurologists to the Symposium Neuroradiologicum, and hopes for a good attendance and a lively exchange of experiences and ideas.

ORGANIZING COMMITTEE:

President: Professor Erik Lindgren, Stockholm
Vice-president: Professor Olle Olsson, Lund
Secretary: Docent Åke Lindbom, Stockholm
Treasurer: Doctor Sven Odén, Stockholm

CORRESPONDENCE ADDRESS:

Secretary of the Symposium Neuroradiologicum,
Serafimerlasarettet,
Stockholm K.
Sweden.